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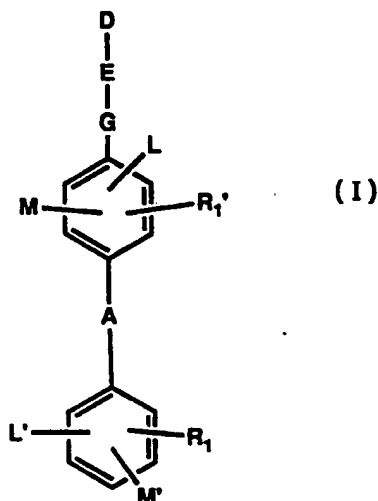


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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(54) Title: ANGIOTENSIN II RECEPTOR ANTAGONISTS



(57) Abstract

Compounds are disclosed having formula (I). The compounds of the invention are angiotensin II receptor antagonists.

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## **ANGIOTENSIN II RECEPTOR ANTAGONISTS**

### **Technical Field**

This invention relates to compounds and compositions which block angiotensin II receptors, processes for making such compounds, synthetic intermediates employed in these processes and a method of treating hypertension, edema, renal failure, benign prostatic hypertrophy, diabetic nephropathy, Alzheimer's disease or congestive heart failure with such compounds. The present invention also relates to compositions and a method for treating glaucoma, preventing or treating atherosclerosis, preventing or treating stroke and treatment of a variety of obesity-related disorders with such compounds. The present invention also relates to compositions and a method for treating CNS disorders.

### **Background of the Invention**

Blood pressure is regulated by a multitude of interrelated factors involving neural, vascular and volume-related effects. The renin-angiotensin system (RAS) is one of the important blood pressure regulating systems.

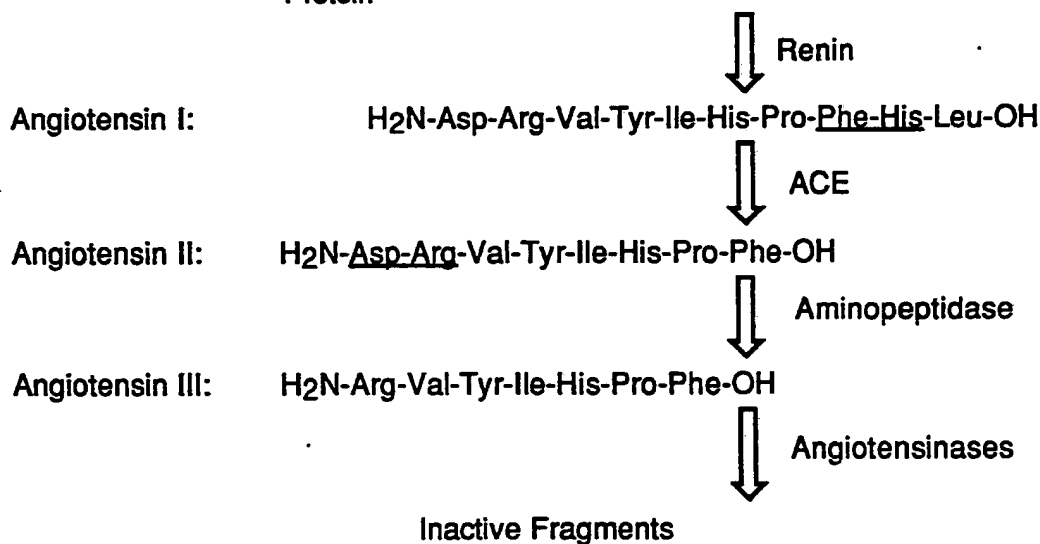
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The RAS functions as shown in the scheme below. Low renal perfusion pressure stimulates the juxtaglomerular cells of the kidney to produce the proteolytic enzyme renin. This enzyme acts on a circulating protein, angiotensinogen, cleaving off a decapeptide angiotensin I. Angiotensin I is then cleaved to the octapeptide angiotensin II by angiotensin converting enzyme (ACE). Angiotensin II is the most powerful pressor substance in the RAS. Angiotensin II binds to vascular smooth muscle receptors and induces vasoconstriction, but has little or no stimulating action on the heart.

### Renin-Angiotensin System

Human

Angiotensinogen: H<sub>2</sub>N-Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu-Val-Ile-His-Protein



Inhibitors of renin (for example enalkiren) and inhibitors of ACE (for example, captopril and enalapril) have clinical efficacy in treating hypertension

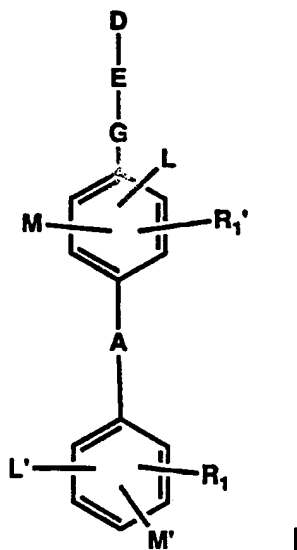
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and congestive heart failure. ACE inhibitors, however, have reported side effects including cough and skin rash.

Peptidyl and non-peptidyl angiotensin II receptor antagonists are known. The peptidyl compound saralasin or [Sar<sup>1</sup>,Ala<sup>8</sup>] angiotensin II has been found to be a potent antagonist of the actions of angiotensin II. Saralasin, however, has several disadvantages. Because it is a peptide, saralasin has very poor oral bioavailability. The use of saralasin, therefore, is limited to administration to hospitalized patients by continuous intravenous infusion. Saralasin is also known to cause an initial increase in blood pressure after intravenous administration due to its activity as an angiotensin receptor agonist. Therefore, non-peptidyl angiotensin II receptor antagonists are preferred.

### Disclosure of the Invention

In accordance with the present invention, there are compounds of the formula I:



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wherein

A is

- (i) a covalent bond,
- (ii) -O-,
- (iii) -C(O)-,
- (iv) -CH<sub>2</sub>-,
- (v) -S-, -S(O)- or -S(O)<sub>2</sub>-;

E-G is

- (i) -N(R<sub>5</sub>)-,
- (ii) -O-,
- (iii) -S-,
- (iv) -N(R<sub>5</sub>)-CH(R<sub>5</sub>)-,
- (v) -O-CH(R<sub>5</sub>)-,
- (vi) -S-CH(R<sub>5</sub>)-,
- (vii) -C(R<sub>5</sub>') (R<sub>5</sub>)-CH(R<sub>5</sub>)-,
- (viii) -CH(R<sub>5</sub>)-C(R<sub>5</sub>') (R<sub>5</sub>)-,
- (ix) -CH(R<sub>5</sub>)-N(R<sub>5</sub>)-,
- (x) -CH(R<sub>5</sub>)-O-,
- (xi) -CH(R<sub>5</sub>)-S-,
- (xii) -N(R<sub>5</sub>)-N(R<sub>5</sub>)-,
- (xiii) -C(R<sub>5</sub>)=C(R<sub>5</sub>)- or
- (xiv) -CH(R<sub>5</sub>)-C(R<sub>5</sub>') (R<sub>5</sub>)-N(R<sub>5</sub>)- wherein at each occurrence R<sub>5</sub> is independently selected from hydrogen, loweralkyl, alkoxy-substituted loweralkyl, halo-substituted loweralkyl, carboxy-substituted loweralkyl, heterocyclic-substituted loweralkyl, alkenyl, alkynyl, cycloalkyl or cycloalkylalkyl and R<sub>5</sub>' is hydrogen, halo, hydroxy, carboxy, alkoxy or thioalkoxy;

L, L', M and M' are independently selected from

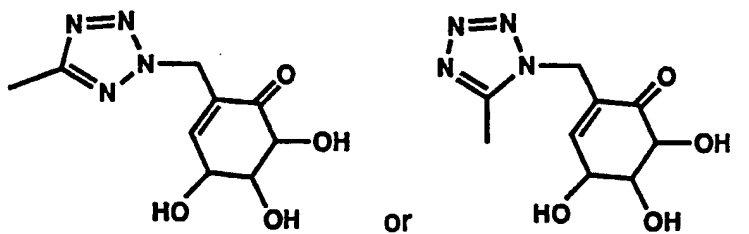
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- (i) hydrogen,
- (ii) loweralkyl,
- (iii) halo-substituted loweralkyl,
- (iv) halo,
- (v) -CN,
- (vi) -NO<sub>2</sub>,
- (vii) -OH,
- (viii) hydroxy-substituted loweralkyl,
- (ix) alkoxy-substituted loweralkyl,
- (x) -NH<sub>2</sub>,
- (xi) alkylamino,
- (xii) dialkylamino,
- (xiii) -SH,
- (xiv) alkoxy and
- (xv) thioalkoxy;

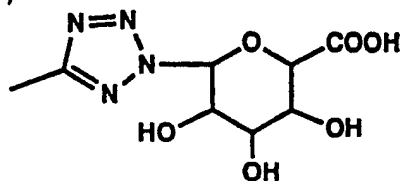
R<sub>1</sub> and R<sub>1</sub>' are independently selected from

- (i) tetrazolyl,

(ii)



(iii)





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- (iv)  $\text{-NH-C(=N(R}_{50a}\text{))}(R_{51a})$  wherein  $R_{50a}$  is hydrogen,  $\text{-CN}$  or  $\text{-NO}_2$  and  $R_{51a}$  is hydrogen, loweralkyl, alkylamino, dialkylamino, alkoxy or thioalkoxy,
- (v)  $\text{-NH}(R_{51b})$  wherein  $R_{51b}$  is a 5-membered aromatic heterocyclic ring wherein the heterocyclic ring contains 1, 2, 3 or 4 nitrogen atoms or 1 nitrogen atom and 1 oxygen atom or 2 nitrogen atoms and 1 oxygen atom or 1 oxygen atom and 1 sulfur atom and wherein the 5-membered heterocyclic ring is unsubstituted or substituted with a substituent selected from amino, alkylamino, dialkylamino, hydroxy, alkoxy, thioalkoxy, halo, loweralkyl and halo-substituted loweralkyl,
- (vi)  $\text{-COOR}_6$  or  $\text{-CH}_2\text{COOR}_6$  wherein  $R_6$  is hydrogen or a carboxy-protecting group or
- (vii)  $\text{-NHS(O)}_2R_7$  or  $\text{-CH}_2\text{NHS(O)}_2R_7$  or  $\text{-NHC(O)}R_{7a}$  or  $\text{-CH}_2\text{NHC(O)}R_{7a}$  wherein  $R_7$  is loweralkyl, halo-substituted loweralkyl or  $\text{-NR}_{7b}R_{7c}$  wherein  $R_{7b}$  and  $R_{7c}$  are independently selected from hydrogen and loweralkyl and  $R_{7a}$  is loweralkyl, halo-substituted loweralkyl, amino, alkylamino, dialkylamino or  $\text{-COOH}$ ;
- (viii)  $\text{-C(O)NR}_{50}R_{51}$  or  $\text{-CH}_2\text{C(O)NR}_{50}R_{51}$  or  $\text{-NHC(O)NR}_{50}R_{51}$  or  $\text{-CH}_2\text{NHC(O)NR}_{50}R_{51}$  or  $\text{-NHC(S)NR}_{50}R_{51}$  or  $\text{-CH}_2\text{NHC(S)NR}_{50}R_{51}$  wherein  $R_{50}$  and  $R_{51}$  are independently selected from hydrogen, loweralkyl, hydroxy, alkoxy, hydroxy-substituted loweralkyl, alkoxy-substituted loweralkyl, alkoxy-substituted alkoxy and  $\text{-S(O)}_2R_{50a}$  wherein  $R_{50a}$  is loweralkyl or aryl, or  $R_{50}$  and  $R_{51}$  taken together with the nitrogen atom to which they are attached form a 5- to 7-membered aliphatic heterocycle;
- (ix)  $\text{-CH}_2\text{OR}_{52}$  wherein  $R_{52}$  is selected from hydrogen, loweralkyl and  $\text{-C(O)R}_{53}$  wherein  $R_{53}$  is hydrogen, loweralkyl or aryl;
- (x)  $\text{-CH(OH)R}_{52a}$  or  $\text{-C(O)R}_{52a}$  wherein  $R_{52a}$  is loweralkyl, halo-substituted loweralkyl,  $\text{-CF}_2\text{COOR}_{53a}$  or  $\text{-CH}_2\text{COOR}_{53a}$  wherein  $R_{53a}$  is hydrogen or a carboxy-protecting group,
- (xii)  $\text{-CH}_2\text{NR}_{54}R_{55}$  wherein  $R_{54}$  is selected from hydrogen, loweralkyl,

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-C(O)R<sub>56</sub>, -C(O)NR<sub>56</sub>R<sub>57</sub> and -S(O)<sub>2</sub>R<sub>58</sub> wherein R<sub>56</sub> is selected from hydrogen, loweralkyl and aryl and R<sub>58</sub> is selected from lower alkyl and halo-substituted loweralkyl and wherein R<sub>55</sub> and R<sub>57</sub> are independently selected from hydrogen, loweralkyl, hydroxy and alkoxy;

(xiii) -SO<sub>3</sub>H, -OSO<sub>3</sub>H or -CH<sub>2</sub>SO<sub>3</sub>H,

(xiv) -OPO<sub>3</sub>H<sub>2</sub>, -PO<sub>3</sub>H<sub>2</sub> or -CH<sub>2</sub>PO<sub>3</sub>H<sub>2</sub>,

(xv) -SO<sub>2</sub>NR<sub>50</sub>R<sub>51</sub> or -CH<sub>2</sub>SO<sub>2</sub>NR<sub>50</sub>R<sub>51</sub> wherein R<sub>50</sub> and R<sub>51</sub> are defined as above and

(xvi) -C(O)NHSO<sub>2</sub>R<sub>60</sub>, -C(O)NHC(O)R<sub>60</sub> or -C(O)NHNHSO<sub>2</sub>R<sub>60</sub> wherein R<sub>60</sub> is loweralkyl, halo-substituted loweralkyl or aryl;

with the proviso that one of R<sub>1</sub> and R<sub>1</sub>' is hydrogen, but R<sub>1</sub> and R<sub>1</sub>' are not both hydrogen;

and

D is a bicyclic heterocycle comprising a 6-membered ring fused to another 6-membered ring, the bicyclic heterocycle comprising at least one heteroatom selected from N, O and S; each of the 6-membered rings of the bicyclic heterocycle independently comprising 0, 1, 2 or 3 nitrogen atoms or 1 nitrogen atom and 1 oxygen atom or 1 nitrogen atom and 1 sulfur atom or 1 oxygen atom and 1 sulfur atom or 2 oxygen atoms or 2 sulfur atoms or 1 oxygen atom or 1 sulfur atom, the remaining ring atoms being carbon atoms and each of the 6-membered rings of the bicyclic heterocycle comprising 0, 1, 2 or 3 double bonds; the nitrogen atoms of the bicyclic heterocycle can be substituted with a substituent R<sub>2</sub> wherein at each occurrence R<sub>2</sub> is independently selected from hydrogen, loweralkyl, carboxy-substituted loweralkyl or alkoxycarbonyl-substituted loweralkyl; the nitrogen atoms of the bicyclic heterocycle can be oxidized; one or two carbon atoms of the bicyclic heterocycle can be substituted with an oxo (=O) substituent and the sulfur atoms of the bicyclic heterocycle can be substituted with one or two oxo (=O) substituents; the bicyclic heterocycle can be substituted with one,

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two or three substituents independently selected from  $R_3$  and  $R_4$ ,  $R_3$  being bonded to a carbon atom or a nitrogen atom of the bicyclic heterocycle and  $R_4$  being bonded to a carbon atom or a nitrogen atom of the bicyclic heterocycle, wherein

$R_3$  is

- (i) hydrogen,
- (ii) loweralkyl,
- (iii) halo,
- (iv) halo-substituted loweralkyl,
- (v) thioalkoxy,
- (vi) alkoxy-substituted loweralkyl,
- (vii) thioalkoxy-substituted loweralkyl,
- (viii) aryl,
- (ix) arylalkyl,
- (x)  $-\text{NO}_2$ ,
- (xi)  $-\text{COOR}_8$  wherein  $R_8$  is hydrogen or a carboxy-protecting group,
- (xii)  $-\text{OR}_9$  wherein  $R_9$  is hydrogen, loweralkyl, halo-substituted loweralkyl, aryl, arylalkyl, heterocyclic-substituted loweralkyl or  $-\text{C(O)}\text{R}_{10}$  wherein  $\text{R}_{10}$  is loweralkyl, halo-substituted loweralkyl,  $-\text{PO}_3\text{H}_2$  or  $-\text{NR}_{11}\text{R}_{12}$  wherein  $\text{R}_{11}$  and  $\text{R}_{12}$  are independently selected from hydrogen and loweralkyl and
- (xiii)  $-\text{NR}_{13}\text{R}_{14}$  or  $-\text{CH}_2\text{NR}_{13}\text{R}_{14}$  wherein  $\text{R}_{13}$  and  $\text{R}_{14}$  are independently selected from (1) hydrogen, (2) lower alkyl, (3) arylalkyl, (4)  $-\text{C(O)}\text{R}_{15}$ , (5)  $-\text{S(O)}_2\text{R}_{15}$  wherein  $\text{R}_{15}$  is loweralkyl or halo-substituted loweralkyl and (6)  $-\text{R}_{16}-\text{R}_{17}$  wherein  $\text{R}_{16}$  is alkylene and  $\text{R}_{17}$  is
  - (a)  $-\text{NR}_{18}\text{R}_{19}$  wherein  $\text{R}_{18}$  and  $\text{R}_{19}$  are independently selected from hydrogen and loweralkyl or
  - (b) unsubstituted or loweralkyl substituted aziridinyl, azetidiny, pyrrolidinyl, piperidinyl, piperazinyl,

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morpholiny, thiomorpholiny, pyridiny or pyrimidiny,  
or R<sub>13</sub> and R<sub>14</sub> taken together with the nitrogen atom to  
which they are attached form a 5- to 7-membered aliphatic  
heterocycle and

R<sub>4</sub> is

- (i) hydrogen,
- (ii) loweralkyl,
- (iii) halo-substituted loweralkyl,
- (iv) -CN,
- (v) -NO<sub>2</sub>,
- (vi) -NH<sub>2</sub>,
- (vii) -NH-C(=N(R<sub>25a</sub>))(R<sub>26a</sub>) wherein R<sub>25a</sub> is hydrogen, -CN or -NO<sub>2</sub> and R<sub>26a</sub> is hydrogen, loweralkyl, alkylamino, dialkylamino, alkoxy or thioalkoxy,
- (viii) -NH(R<sub>26b</sub>) wherein R<sub>26b</sub> is a 5-membered aromatic heterocyclic ring wherein the heterocyclic ring contains 1, 2, 3 or 4 nitrogen atoms or 1 nitrogen atom and 1 oxygen atom or 2 nitrogen atoms and 1 oxygen atom or 1 oxygen atom and 1 sulfur atom and wherein the 5-membered heterocyclic ring is unsubstituted or substituted with a substituent selected from amino, alkylamino, dialkylamino, hydroxy, alkoxy, thioalkoxy, halo, loweralkyl and halo-substituted loweralkyl,
- (ix) -CHO or -CH(=N-OH),
- (x) tetrazolyl,
- (xi) -NHS(O)<sub>2</sub>R<sub>20</sub> or -CH<sub>2</sub>NHS(O)<sub>2</sub>R<sub>20</sub> or -NHC(O)R<sub>21</sub> or -N(OH)C(O)R<sub>21</sub> or -CH<sub>2</sub>NHC(O)R<sub>21</sub> or -CH<sub>2</sub>N(OH)C(O)R<sub>21</sub> wherein R<sub>20</sub> is loweralkyl, halo-substituted loweralkyl or -NR<sub>27a</sub>R<sub>27b</sub> wherein R<sub>27a</sub> and R<sub>27b</sub> are independently selected from hydrogen, -OH and loweralkyl and R<sub>21</sub> is loweralkyl, halo-substituted loweralkyl, amino, alkylamino, dialkylamino or -COOH,
- (xii) -CH(OH)R<sub>22</sub> or -C(O)R<sub>22</sub> wherein R<sub>22</sub> is loweralkyl, halo-

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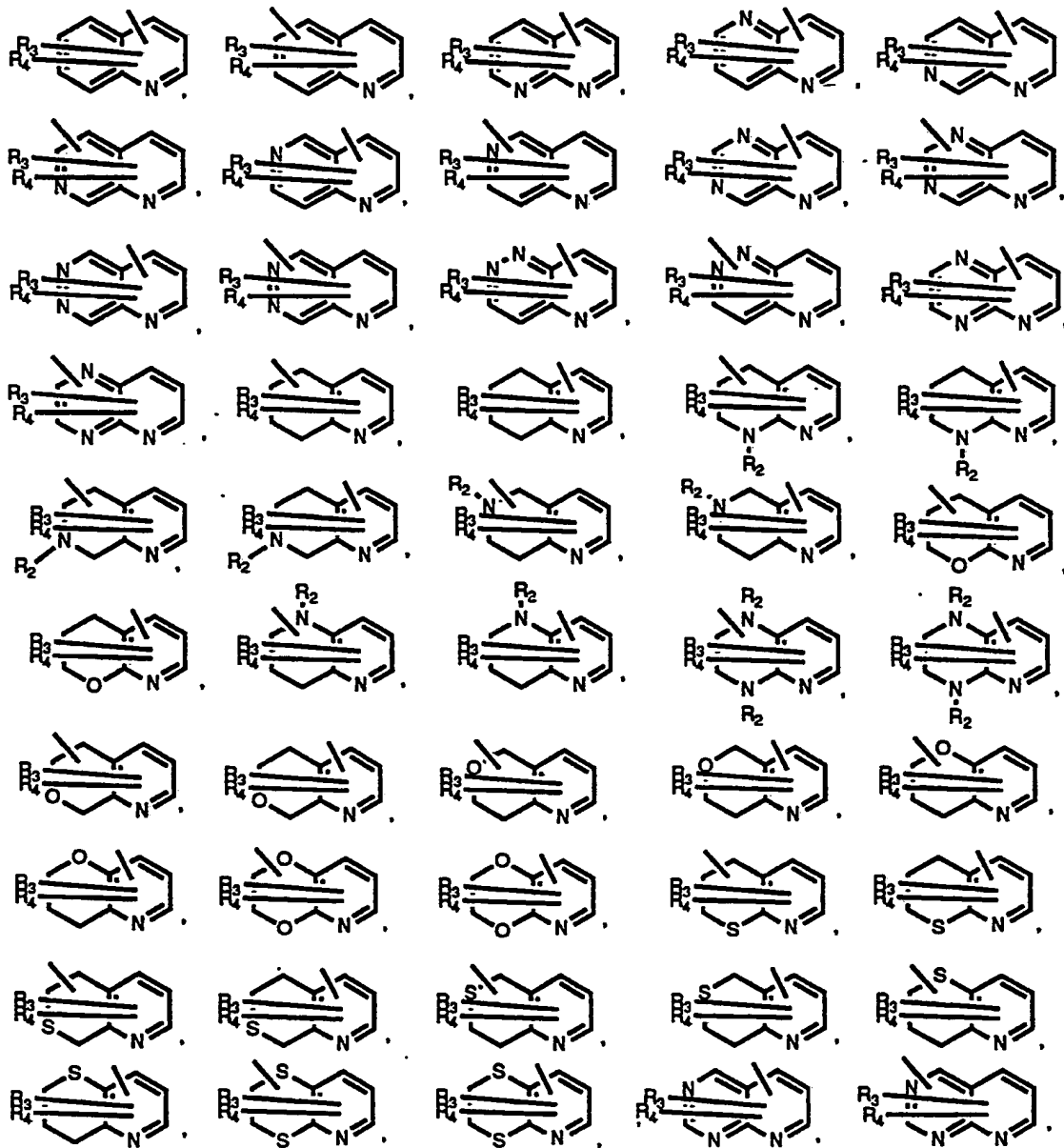
- substituted loweralkyl,  $-\text{CF}_2\text{COOR}_{23}$  or  $-\text{CH}_2\text{COOR}_{23}$   
wherein  $\text{R}_{23}$  is hydrogen or a carboxy-protecting group,
- (xiii)  $-\text{COOR}_{24}$  or  $-\text{CH}_2\text{COOR}_{24}$  wherein  $\text{R}_{24}$  is hydrogen or a  
carboxy-protecting group,
- (xiv)  $-\text{C}(\text{O})\text{NR}_{25}\text{R}_{26}$  or  $-\text{CH}_2\text{C}(\text{O})\text{NR}_{25}\text{R}_{26}$  or  $-\text{NHC}(\text{O})\text{NR}_{25}\text{R}_{26}$   
or  $-\text{CH}_2\text{NHC}(\text{O})\text{NR}_{25}\text{R}_{26}$  or  $-\text{NHC}(\text{S})\text{NR}_{25}\text{R}_{26}$   
or  $-\text{CH}_2\text{NHC}(\text{S})\text{NR}_{25}\text{R}_{26}$  wherein  $\text{R}_{25}$  and  $\text{R}_{26}$  are  
independently selected from hydrogen, loweralkyl,  
hydroxy, alkoxy, hydroxy-substituted loweralkyl,  
alkoxy-substituted loweralkyl, alkoxy-substituted  
alkoxy and  $-\text{S}(\text{O})_2\text{R}_{28a}$  wherein  $\text{R}_{28a}$  is loweralkyl or aryl, or  $\text{R}_{25}$  and  
 $\text{R}_{26}$  taken together with the nitrogen atom to which they are attached  
form a 5- to 7- membered aliphatic heterocycle;
- (xv)  $-\text{CH}_2\text{OR}_{27}$  wherein  $\text{R}_{27}$  is selected from hydrogen,  
loweralkyl and  $-\text{C}(\text{O})\text{R}_{28}$  wherein  $\text{R}_{28}$  is hydrogen,  
loweralkyl or aryl;
- (xvi)  $-\text{CH}_2\text{NR}_{29}\text{R}_{30}$  wherein  $\text{R}_{29}$  is selected from hydrogen,  
loweralkyl,  $-\text{C}(\text{O})\text{R}_{31}$ ,  $-\text{C}(\text{O})\text{NR}_{31}\text{R}_{32}$  and  $-\text{S}(\text{O})_2\text{R}_{33}$   
wherein  $\text{R}_{31}$  is selected from hydrogen, loweralkyl and  
aryl and  $\text{R}_{33}$  is selected from loweralkyl and halo-  
substituted loweralkyl and wherein  $\text{R}_{30}$  and  $\text{R}_{32}$  are  
independently selected from hydrogen, loweralkyl,  
hydroxy and alkoxy;
- (xvii)  $-\text{SO}_3\text{H}$ ,  $-\text{OSO}_3\text{H}$  or  $-\text{CH}_2\text{SO}_3\text{H}$ ,
- (xviii)  $-\text{OPO}_3\text{H}$ ,  $-\text{PO}_3\text{H}_2$  or  $-\text{CH}_2\text{PO}_3\text{H}_2$ ,
- (xix)  $-\text{SO}_2\text{NR}_{25}\text{R}_{26}$  or  $-\text{CH}_2\text{SO}_2\text{NR}_{25}\text{R}_{26}$  wherein  $\text{R}_{25}$  and  $\text{R}_{26}$   
are defined as above and
- (xx)  $-\text{C}(\text{O})\text{NHSO}_2\text{R}_{59}$ ,  $-\text{C}(\text{O})\text{NHC}(\text{O})\text{R}_{59}$  or  $-\text{C}(\text{O})\text{NHNHSO}_2\text{R}_{59}$   
wherein  $\text{R}_{59}$  is loweralkyl, halo-substituted loweralkyl or  
aryl;

or a pharmaceutically acceptable salt or prodrug thereof.

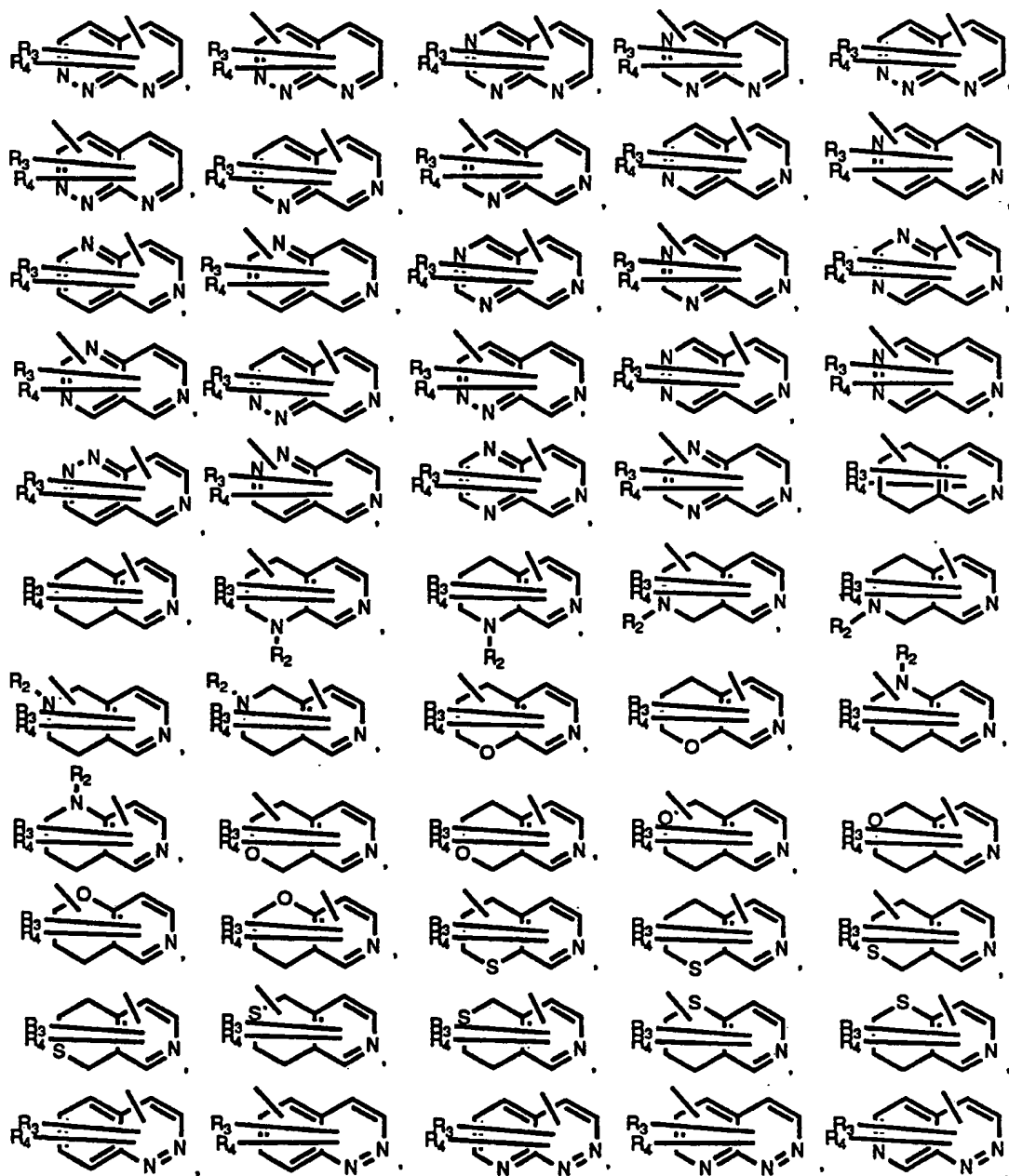
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Preferred compounds of the invention are compounds wherein D is a substituted quinolinyl group, a substituted naphthyridinyl group, a substituted pteridinyl group, a substituted pyridopyrimidinyl group, a substituted quinazolinyl group, a substituted pyridopyrazinyl group, a substituted pyridotriazinyl group, a substituted pyrimidopyridazinyl group, a substituted pyridopyrazinyl group or a substituted pyrazinopyridazinyl group.

Representative bicyclic heterocycle substituents of the compounds of this invention are:

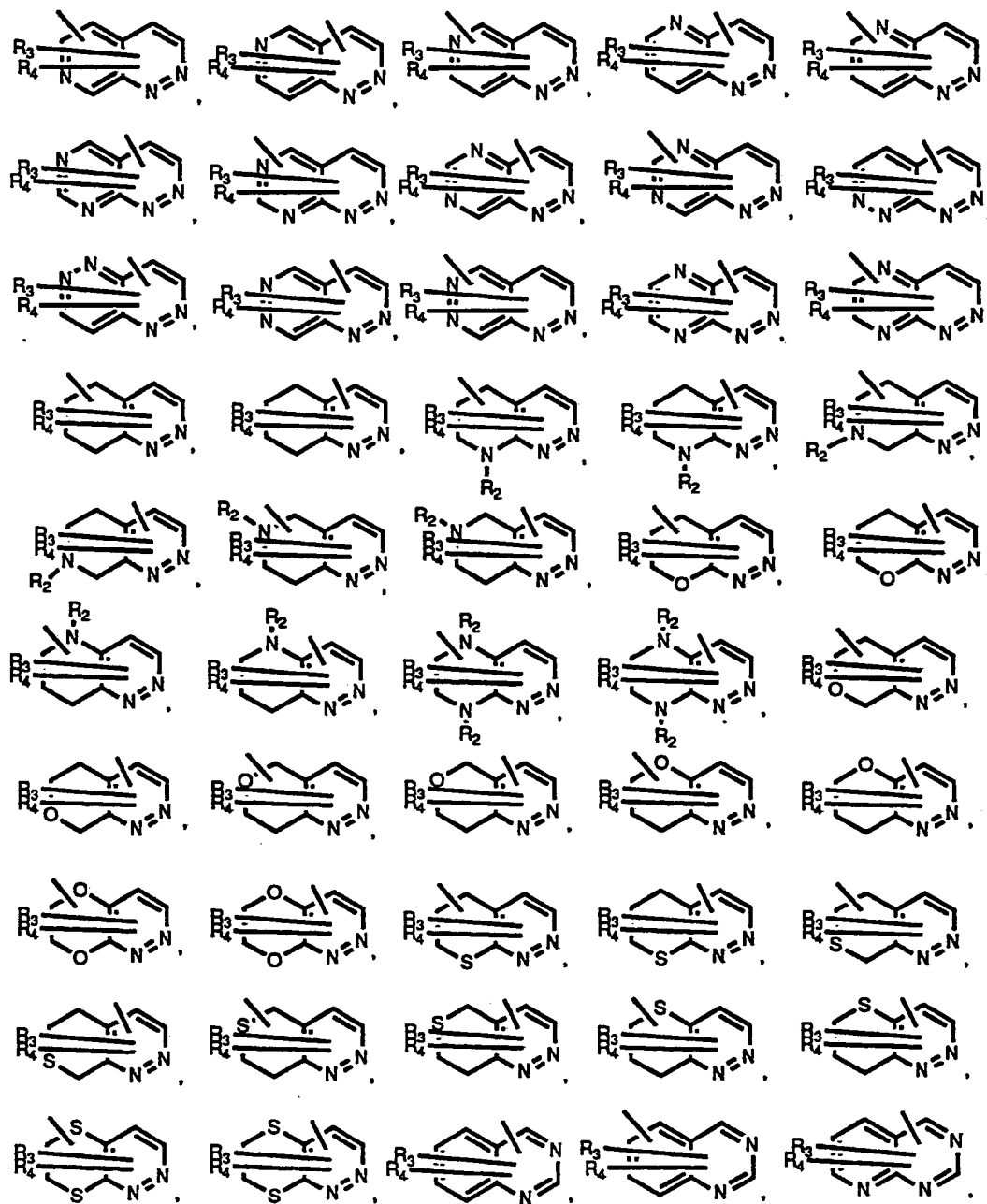


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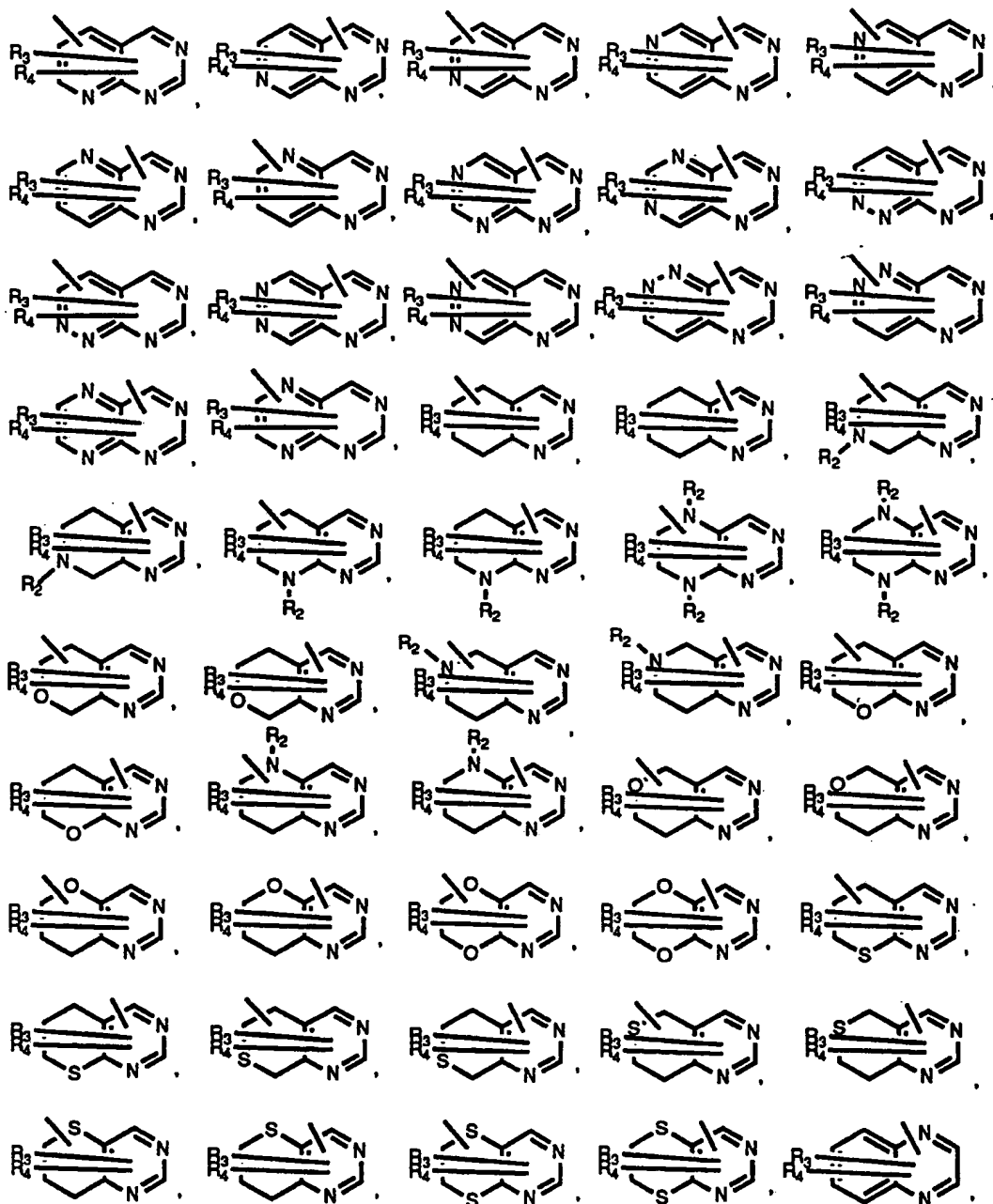




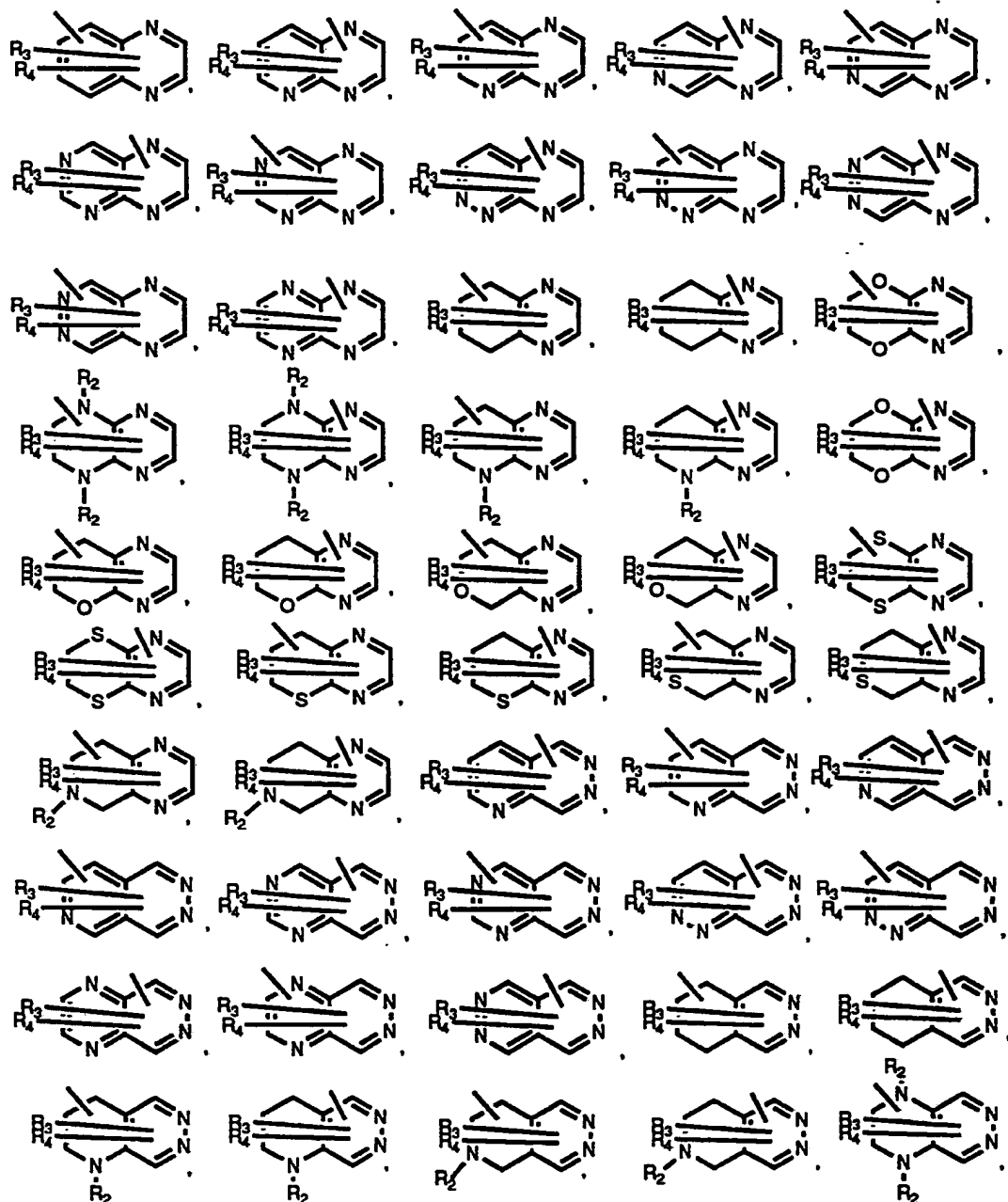
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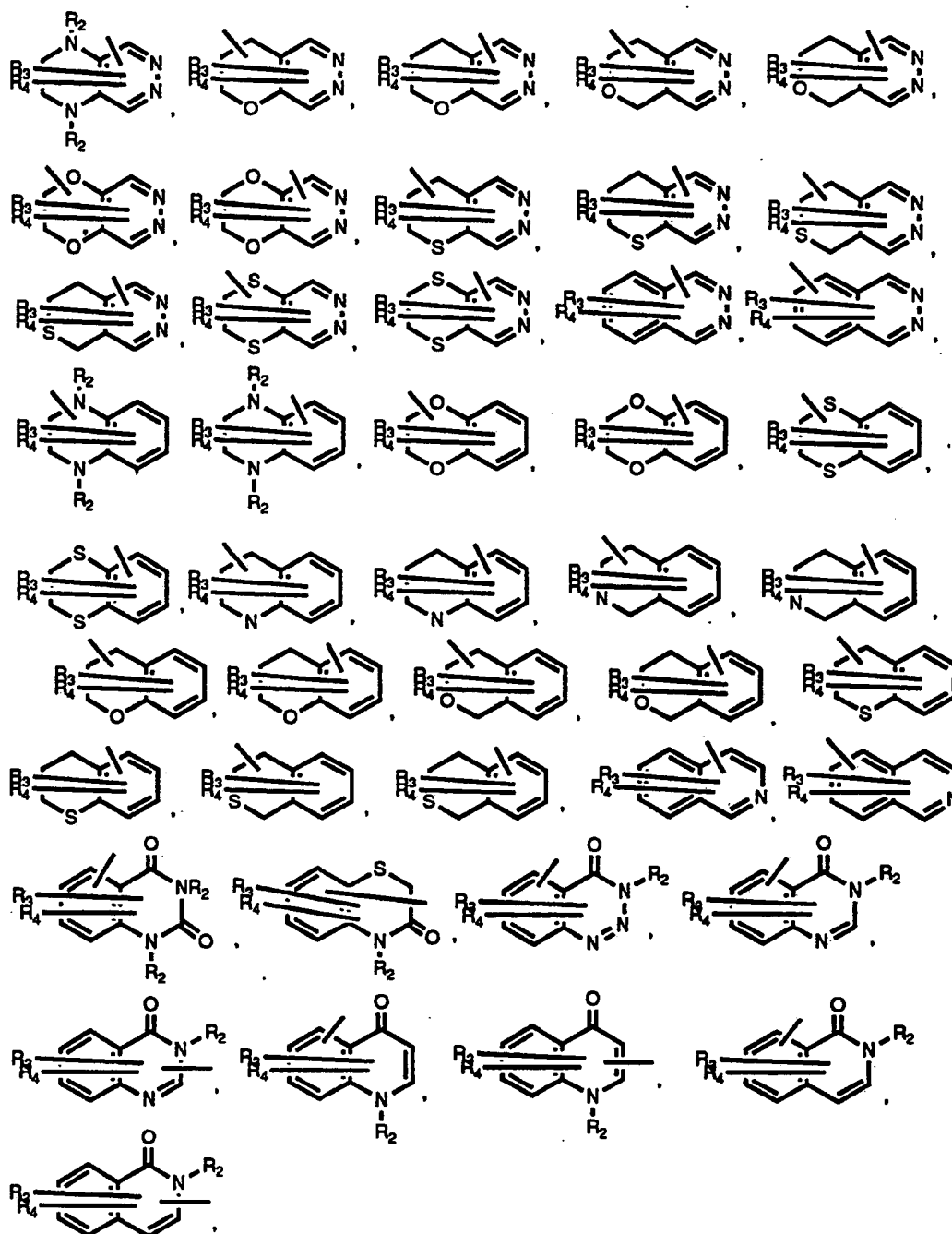
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and the like.

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The term "loweralkyl" as used herein refers to branched or straight chain alkyl groups comprising one to ten carbon atoms, including methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, neopentyl and the like.

The term "alkenyl" as used herein refers to a branched or straight chain comprising two to ten carbon atoms which has one or more carbon-carbon double bonds, including vinyl, propenyl, butenyl and the like.

The term "alkynyl" as used herein refers to a branched or straight chain comprising two to ten carbon atoms which has one or more carbon-carbon triple bonds, including ethynyl, propynyl, butynyl and the like.

The term "cycloalkyl" as used herein refers to an alicyclic group comprising from 3 to 7 carbon atoms, including cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

The term "cycloalkylalkyl" as used herein refers to a loweralkyl radical to which is appended a cycloalkyl group, including cyclopentylmethyl, cyclohexylmethyl and the like.

The term "alkylene" as used herein refers to a 1 to 10 carbon straight or branched chain di-radical, including  $-\text{CH}_2-$ ,  $-\text{CH}(\text{CH}_3)-$ ,  $-\text{CH}_2\text{CH}_2\text{CH}_2-$ ,  $-\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_2-$  and the like.

The term "halo-substituted loweralkyl" refers to a loweralkyl radical in which one or more of the hydrogen atoms are replaced by halogen, including chloromethyl, fluoroethyl, trifluoromethyl, pentafluoroethyl and the like.

The term "hydroxy-substituted loweralkyl" refers to a loweralkyl radical to which is appended one or two hydroxy ( $-\text{OH}$ ) groups.

The term "halogen" or "halo" as used herein refers to I, Br, Cl or F.

The term "alkoxy" refers to  $\text{R}_{34}\text{O}-$  wherein  $\text{R}_{34}$  is a loweralkyl or benzyl group. Representative examples of alkoxy groups include methoxy, ethoxy, t-butoxy, benzyloxy and the like.

The term "thioalkoxy" as used herein refers to  $\text{R}_{35}\text{S}-$  wherein  $\text{R}_{35}$  is a loweralkyl or benzyl group.

The term "alkoxy-substituted loweralkyl" as used herein refers to a loweralkyl radical to which is appended an alkoxy group.

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The term "thioalkoxy-substituted loweralkyl" as used herein refers to a loweralkyl radical to which is appended a thioalkoxy group. Representative thioalkoxy-substituted loweralkyl groups include methylthiomethyl, methylthioethyl, ethylthioethyl, propylthiomethyl and the like.

The term "hydroxy-substituted loweralkyl" as used herein refers to a loweralkyl radical to which is appended one or two hydroxy (-OH) groups.

The term "carboxy-substituted loweralkyl" as used herein refers to a loweralkyl radical to which is appended a carboxy group (-COOH), including carboxymethyl, carboxyethyl and the like.

The term "alkoxycarbonyl" as used herein refers to  $-C(O)OR_{36}$  wherein  $R_{36}$  is a carboxy-protecting group.

The term "alkoxycarbonyl-substituted loweralkyl" as used herein refers to a loweralkyl radical to which is appended an alkoxycarbonyl group.

The term "alkoxy-substituted alkoxy" as used here refers to an alkoxy radical to which is appended another alkoxy radical, including methoxymethoxy, methoxy ethoxy, ethoxyethoxy and the like.

The term "alkylamino" as used herein refers to  $-NHR_{37}$  wherein  $R_{37}$  is a loweralkyl group.

The term "dialkylamino" as used herein refers to  $-NR_{38}R_{39}$  wherein  $R_{38}$  and  $R_{39}$  are independently selected from loweralkyl.

The term "alkanoyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended  $-OC(O)R_{40}$  wherein  $R_{40}$  is loweralkyl.

The term "aroyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended  $-OC(O)R_{41}$  wherein  $R_{41}$  is aryl.

The term "alkoxycarbonylalkyl" as used herein refers to a loweralkyl radical to which is appended an alkoxycarbonyl group.

The term "alkoxycarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended  $-OC(O)OR_{42}$  wherein  $R_{42}$  is loweralkyl or cycloalkyl.

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The term "alkoxycarbonylaminoalkyl" as used herein refers to a loweralkyl radical to which is appended  $\text{-NHC(O)OR}_{43}$  wherein  $R_{43}$  is loweralkyl.

The term "alkylaminocarbonylaminoalkyl" as used herein refers to a loweralkyl radical to which is appended  $\text{-NHC(O)NHR}_{44}$  wherein  $R_{44}$  is loweralkyl.

The term "alkanoylaminoalkyl" as used herein refers to a loweralkyl radical to which is appended  $\text{-NHC(O)R}_{45}$  wherein  $R_{45}$  is loweralkyl.

The term "heterocycliccarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended  $\text{-OC(O)R}_{46}$  wherein  $R_{46}$  is a heterocyclic group.

The term "aryl" as used herein refers to a phenyl or a  $C_9$  or  $C_{10}$  bicyclic carbocyclic ring system having one or more aromatic rings, including naphthyl, tetrahydronaphthyl, indanyl, indenyl and the like. Aryl groups can be unsubstituted or substituted with one, two or three substituents independently selected from loweralkyl, halo-substituted loweralkyl, alkoxy, thioalkoxy, alkoxycarbonyl, hydroxy, halo, mercapto, nitro, amino, alkylamino, dialkylamino, carboxaldehyde, carboxy and carboxamide.

The term "arylalkyl" as used herein refers to a loweralkyl radical to which is appended an aryl group. Representative arylalkyl groups include benzyl, phenylethyl, fluorobenzyl, fluorophenylethyl and the like.

The term "aliphatic heterocycle" as used herein refers to a saturated cyclic group containing 5 to 7 ring atoms and, in particular, at least 1 nitrogen atom in the ring and optionally 1 additional heteroatom selected from S,  $S(O)_2$ , O and N, with the remaining ring atoms being carbon atoms. The ring can be substituted on a carbon atom or a heteroatom, for example, with loweralkyl, alkoxy or alkoxy-substituted alkoxy. Representative aliphatic heterocycles include, pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine, S,S-dioxothiomorpholine, 4-methoxymethoxypiperidine and the like.

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The term "heterocyclic group" or "heterocyclic" as used herein in the context of the terms "heterocyclic-substituted loweralkyl" and "5- to 7-membered aliphatic heterocycle" refers to any 3- or 4-membered ring containing a heteroatom selected from oxygen, nitrogen and sulfur, or a 5-, 6- or 7-membered ring containing one, two or three nitrogen atoms; one nitrogen and one sulfur atom; or one nitrogen and one oxygen atom; wherein the 5-membered ring has 0-2 double bonds and the 6- or 7-membered ring has 0-3 double bonds; wherein the nitrogen and sulfur heteroatoms can optionally be oxidized; wherein the nitrogen heteroatom can optionally be quaternized; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring or another 5-, 6- or 7-membered heterocyclic ring independently as defined above. Heterocyclics include indolyl, quinolyl, isoquinolyl, tetrahydroquinolyl, benzofuryl, benzothienyl, azetidyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, piperidinyl, pyrazinyl, piperazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiomorpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, indolyl, quinolyl, isoquinolyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, furyl, thienyl, triazolyl, benzothienyl, homopiperazinyl, homopiperidinyl, homomorpholinyl and the like.

Heterocyclics can be unsubstituted or monosubstituted or disubstituted with substituents independently selected from hydroxy, halo, oxo (=O), amino, alkylamino, dialkylamino, alkoxy, thioalkoxy, carboxy, alkoxycarbonyl, loweralkyl, cycloalkyl, -OSO<sub>3</sub>H and halo-substituted loweralkyl.

The term "heterocyclic-substituted loweralkyl" as used herein refers to a loweralkyl radical to which is appended a heterocyclic group.

The term "N-protecting group" or "N-protected" as used herein refers to those groups intended to protect an amino group against undesirable reactions during synthetic procedures. Commonly used N-protecting groups are disclosed in Greene, "Protective Groups In Organic Synthesis," (John Wiley & Sons, New York (1981)), which is hereby incorporated by reference. N-



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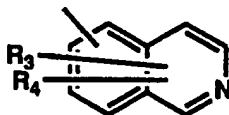
protecting groups comprise carbamates, amides, N-alkyl derivatives, amino acetal derivatives, N-benzyl derivatives, imine derivatives, enamine derivatives and N-heteroatom derivatives. Preferred N-protecting groups are formyl, acetyl, benzoyl, pivaloyl, phenylsulfonyl, benzyl, t-butyloxycarbonyl (Boc), benzyloxycarbonyl (Cbz) and the like.

As used herein, the term "carboxy-protecting group" refers to a carboxy group which has been esterified with one of the commonly used carboxylic acid protecting ester groups employed to block or protect the carboxylic acid functionality while the reactions involving other functional sites of the compound are carried out. Carboxy-protecting groups are disclosed in Greene, "Protective Groups in Organic Synthesis" pp. 152-186 (1981), which is incorporated herein by reference. In addition, a carboxy-protecting group can be used as a prodrug whereby the carboxy-protecting group can be readily cleaved *in vivo*, for example by enzymatic hydrolysis, to release the biologically active parent. T. Higuchi and V. Stella provide a thorough discussion of the prodrug concept in "Pro-drugs as Novel Delivery Systems", Vol 14 of the A.C.S. Symposium Series, American Chemical Society (1975). Such carboxy-protecting groups are well known to those skilled in the art, having been extensively used in the protection of carboxyl groups in the penicillin and cephalosporin fields, as described in U.S. Pat. No. 3,840,556 and 3,719,667, the disclosures of which are incorporated herein by reference. Examples of esters useful as prodrugs for compounds containing carboxyl groups can be found on pages 14-21 of "Bioreversible Carriers in Drug Design: Theory and Application", edited by E.B. Roche, Pergamon Press:New York (1987). Representative carboxy-protecting groups are C<sub>1</sub> to C<sub>8</sub> alkyl (e.g., methyl, ethyl or tertiary butyl and the like), benzyl and substituted derivatives thereof such as alkoxybenzyl or nitrobenzyl groups and the like, dialkylaminoalkyl (e.g., dimethylaminoethyl and the like), alkanoyloxyalkyl groups such as pivaloyloxymethyl or propionyloxymethyl and the like, aroyloxyalkyl, such as benzoyloxyethyl and the like, alkoxycarbonylalkyl, such as methoxycarbonylmethyl, cyclohexyloxycarbonylmethyl and the like, alkoxycarbonyloxyalkyl, such as t-

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butyloxycarbonyloxymethyl and the like, alkoxycarbonylaminoalkyl, such as t-butyloxycarbonylaminoalkyl and the like, alkylaminocarbonylaminoalkyl, such as methylaminocarbonylaminoalkyl and the like, alkanoylaminoalkyl, such as acetylaminoalkyl and the like, heterocycliccarbonyloxyalkyl, such as 4-methylpiperazinyloxymethyl and the like, dialkylaminocarbonylalkyl, such as dimethylaminocarbonylmethyl and the like, (5-(loweralkyl)-2-oxo-1,3-dioxolen-4-yl)alkyl, such as (5-t-butyl-2-oxo-1,3-dioxolen-4-yl)methyl and the like and (5-phenyl-2-oxo-1,3-dioxolen-4-yl)alkyl, such as (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methyl and the like.

When used herein, a formula such as



represents a bicyclic heterocycle where R<sub>3</sub> is bonded to either of the 6-membered rings and R<sub>4</sub> is bonded to either of the 6-membered rings.

When the compounds of formula I contain one asymmetric carbon atom, they can exist as pure enantiomers or mixtures of enantiomers. When the compounds of formula I contain more than one asymmetric carbon atom, they can exist as diastereomers, mixtures of diastereomers, diastereomeric racemates or mixtures of diastereomeric racemates. The present invention includes within its scope all of the isomeric forms. The terms "R" and "S" configuration used herein are as defined by IUPAC 1974 Recommendations for Section E, Fundamental Stereochemistry, Pure Appl. Chem (1976) 45, 13-30.

In addition, in the compounds of the invention, combinations of substituents and/or variables (i.e., A, D, E, G, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, etc.) are permissible only if such combinations result in stable compounds.

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In general, the compounds of this invention can be prepared by the processes illustrated in Schemes I through XXXI. It should be understood that substituents A, D, E, G, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, etc. as used herein correspond to the groups identified by formula (I). P is a protecting group. In the course of synthesis, certain groups present in the molecule, particularly carboxylic acid and tetrazole groups, are protected and deprotected as necessary. The term "protecting group" is well known in the art and refers to substituents on functional groups of compounds undergoing chemical transformation which prevent undesired reactions and degradations during a synthesis; see, for example, T.H. Greene, "Protective Groups in Organic Synthesis", John Wiley & Sons, New York (1981) for methods of introducing and removing appropriate protecting groups. Suitable carboxy-protecting groups include t-butyl and benzyl groups. Suitable tetrazole nitrogen-protecting groups include triphenylmethyl (Tr), benzyl, t-butyl, methoxymethyl, benzyloxymethyl, p-nitrobenzyl, 1-ethoxyethyl and the like.

The compounds of formula (I) may be prepared using the reactions and techniques described in this section. The reactions are performed in a solvent appropriate to the reagents and materials employed and suitable for the transformation being effected. It is understood by those skilled in the art of organic synthesis that the functionality present on the heterocycle and other portions of the molecule must be consistent with the chemical transformation proposed. This will frequently necessitate judgment as to the order of synthetic steps, protecting groups required and deprotection conditions. Throughout the following section, not all compounds of formula (I) falling into a given class may necessarily be prepared by all methods described for that class. Substituents on the starting materials may be incompatible with some of the reaction conditions required in some of the methods described. Such restrictions to the substituents which are compatible with the reaction conditions will be readily apparent to one skilled in the art and alternative methods described must then be used.

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Schemes I - XV illustrate methods of preparing compounds of the invention comprising various -G-E- substituents.

#### Scheme I

Reaction Scheme I illustrates a method of preparing compounds wherein -G-E- is -N(R<sub>5</sub>)-. According to Scheme XVIII, a biphenylamine of Formula 82 is alkylated under standard conditions (e.g., R<sub>5</sub>-X' wherein X' is a leaving group) and then reacted with a chloro-heterocycle to give a compound of Formula 81.

#### Scheme II

According to Scheme II, compounds wherein -G-E- is -O- are prepared by coupling a hydroxy-substituted heterocycle with a bromo-biphenyl compound of Formula 80 in the presence of a copper salt to give a compound of Formula 83.

#### Scheme III

Reaction Scheme III illustrates a method of preparing compounds wherein -G-E- is -S-. According to Scheme XX, a biphenyl thiol of Formula 85 is reacted with a chloro-heterocycle to give a compound of Formula 84.

#### Scheme IV

Reaction Schemes IVA and IVB illustrate alternative methods of preparing compounds wherein -G-E- is -CH<sub>2</sub>-N(R<sub>5</sub>)-. According to Scheme IVA, a biphenylmethylamine of the Formula 86 is reacted with a chloro-heterocycle in the presence of a base, such as triethylamine or lithium hexamethyldisilazide, to give a compound of Formula 87. Alternatively, according to Scheme IVB, a chloro-heterocycle is reacted with a primary amine to give a compound of Formula 88. This secondary amine is reacted with a biphenylmethyl bromide 89 to give a compound of Formula 87.

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#### Scheme V

According to Scheme V, compounds wherein -G-E- is -CH(R<sub>5</sub>)-NH- are prepared by oxidizing a compound of Formula 90 to aldehyde 91. Addition of an organometallic reagent ( e.g., R<sub>5</sub>-M is propyl-Grignard reagent, yields secondary alcohol 92. The alcohol is converted to a leaving group (e.g., X' is a mesylate) which is displaced with a heterocyclic amine to afford a compound of Formula 94.

#### Scheme VI

Reaction Schemes VIA and VIB illustrate alternative methods of preparing compounds wherein -G-E- is -CH(R<sub>5</sub>)-O-. According to Scheme VIA, a compound of Formula 93 having a leaving group X', e.g., mesylate, is reacted with a hydroxy-substituted heterocyclic in the presence of a base to give a compound of Formula 95. Alternatively, according to Scheme VIB, secondary alcohol 92, whose preparation is illustrated in Scheme XXII, is reacted with a chloro-heterocycle in the presence of a base to give a compound of Formula 95.

#### Scheme VII

According to Scheme VII, compounds wherein -G-E- is -CH(R<sub>5</sub>)-S- are prepared by reacting a compound of Formula 93, whose preparation is illustrated in Scheme XXII, with a thiol-substituted heterocycle in the presence of a base to give a compound of Formula 96.

#### Scheme VIII

According to Scheme VIII, compounds wherein -G-E- is -CH<sub>2</sub>-CH(R<sub>5</sub>)- are prepared by reacting a heterocyclic aldehyde of Formula 97 with a Wittig reagent (CH<sub>2</sub>=P(Ph)<sub>3</sub>) to yield vinyl-heterocycle 98. Olefin epoxidation with *m*-chloroperoxybenzoic acid affords epoxide 99. Epoxide 99 is opened with a Grignard reagent 100 prepared from the corresponding biphenylbromide. The resulting alcohol 101 is oxidized (e.g., Swern oxidation) to afford ketone 102. The ketone is reacted with the desired Wittig reagent (e.g., Pr-P(Ph)<sub>3</sub>) to give an

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intermediate olefin which is reduced with hydrogen in the presence of a catalyst (e.g., platinum or palladium) to afford a compound of Formula 103.

#### Scheme IX

According to Scheme IX, compounds wherein -G-E- is  $-\text{CH}(\text{R}_5)-\text{CH}_2-$  are prepared by converting a biphenyl aldehyde of the Formula 91 to a halo-alkylated compound of the Formula 93A (X' is halogen). Compound 93A is converted into Wittig reagent 110 using triphenylphosphine and a suitable base. This Wittig reagent is reacted with heterocyclic aldehyde 97 to give a compound of the Formula 111. This olefin is reduced with hydrogen in the presence of a catalyst such as platinum or palladium to give a compound of the Formula 112.

#### Scheme X

According to Scheme X, compounds wherein -G-E- is  $-\text{N}(\text{R}_5)-\text{CH}_2-$  are prepared by alkylating amine 82 with  $\text{R}_5\text{Cl}$  in the presence of a base. The resulting amine 82a is reductively aminated with aldehyde 97 to give a compound of the Formula 114.

#### Scheme XI

According to Scheme XI, compounds wherein -G-E- is  $-\text{NH}-\text{CH}(\text{R}_5)-$  are prepared by reacting a heterocyclic nitrile 115 with an alkyl Grignard reagent (e.g., propylmagnesium bromide) and then hydrolyzing the intermediate imine to give a ketone of the Formula 116. Reductive amination with a biphenylamine 82 yields a compound of the Formula 117.

#### Scheme XII

According to Scheme XII, compounds wherein -G-E- is  $-\text{O}-\text{CH}(\text{R}_5)-$  are prepared by reacting a heterocyclic aldehyde with an organometallic reagent (e.g.,  $\text{R}_5-\text{M}$  is propylmagnesium bromide) to produce a secondary alcohol of the Formula 120. The alcohol is converted to a leaving group (for example,

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mesylate) and then is coupled with the biphenyl alcohol in the presence of a base to afford a compound of the Formula 121.

#### Scheme XIII

According to Scheme XIII, compounds wherein -G-E- is -S-CH(R<sub>5</sub>)- are prepared by converting a secondary alcohol to a leaving group (e.g., X' is mesylate) and then displacing it with biphenyl thiol 85 in the presence of a base to afford a compound of the Formula 123.

#### Scheme XIV

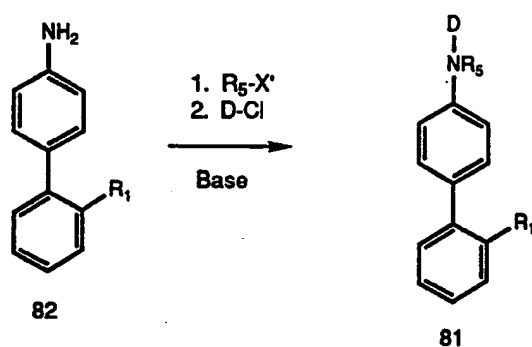
According to Scheme XIV, compounds wherein -G-E- is -NH-N(R<sub>5</sub>)- are prepared by converting a biphenylamine 82 into a urea of the Formula 124. The urea is reacted with bromine in the presence of a base to yield hydrazine 125. Alkylation with an alkyl bromide (e.g., R<sub>5</sub>X' is propyl bromide), followed by displacement of a chloro heterocycle with the secondary amine 125, affords a compound of the Formula 126.

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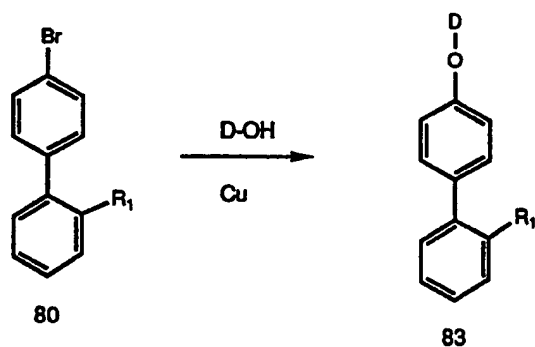
Scheme XV

According to Scheme XV, compounds wherein -G-E- is -N(R<sub>5</sub>)-NH- are prepared by first converting amine 82a to urea 130. Urea 130 is converted to hydrazine 131 by treatment with bromine in base. Hydrazine 131 is reacted with chloro-heterocycle D-Cl to afford a compound of the Formula 132.

## SCHEME I



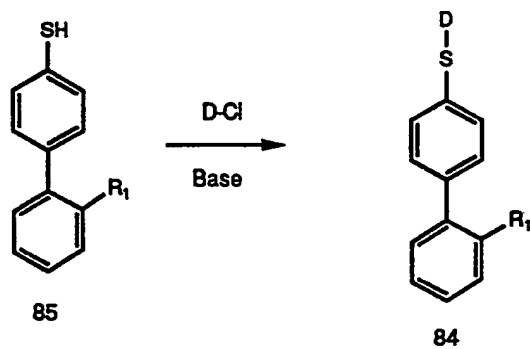
## SCHEME II



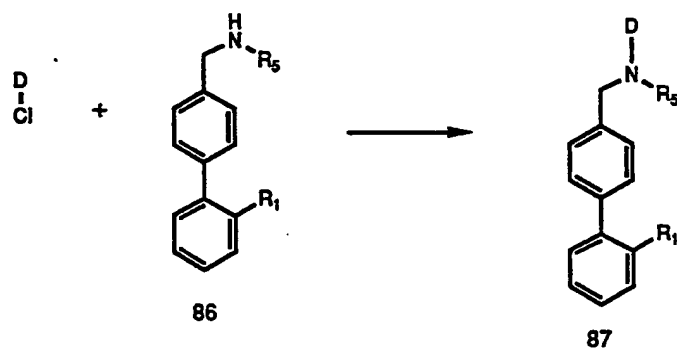


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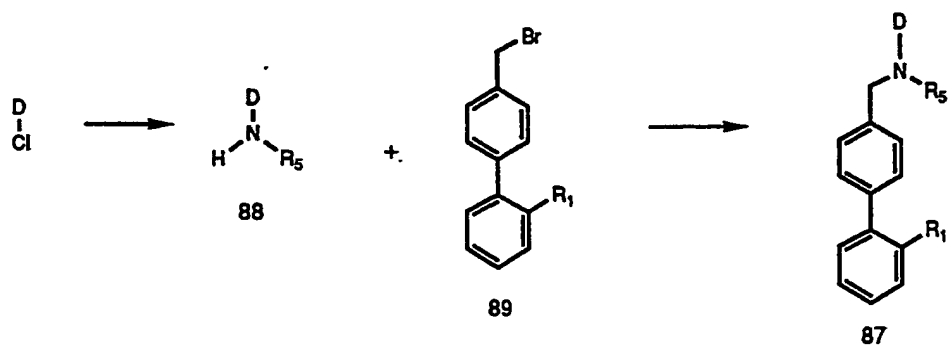
## SCHEME III



## SCHEME IVA

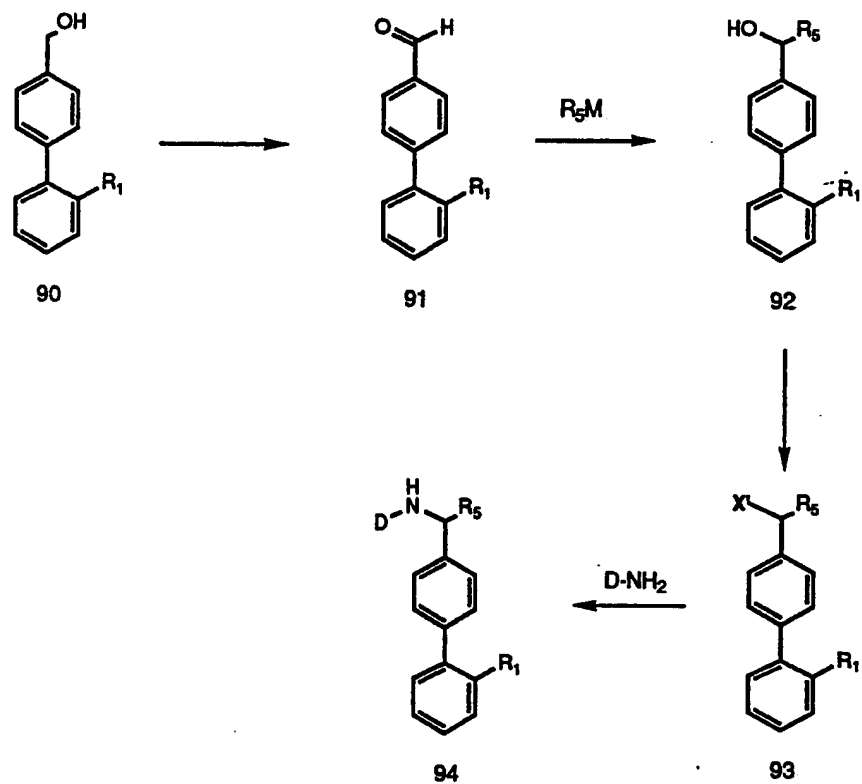


## SCHEME IVB



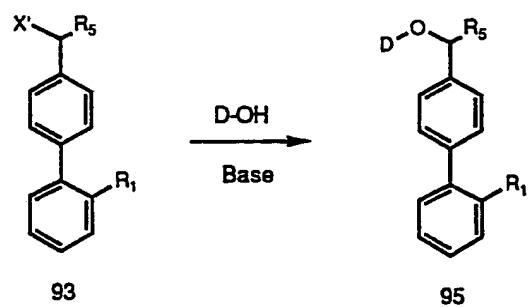
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## SCHEME V

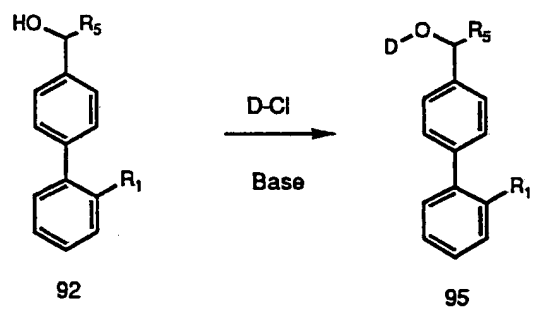


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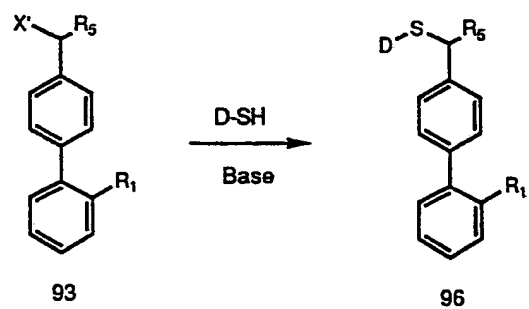
## SCHEME VIA



## SCHEME VIB

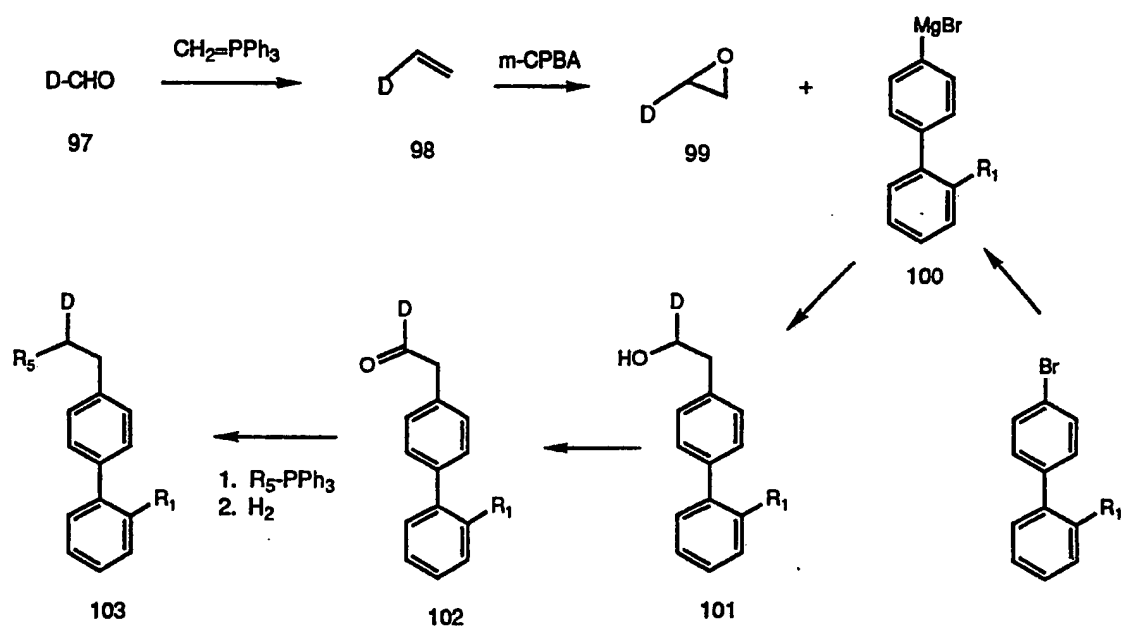


## SCHEME VII



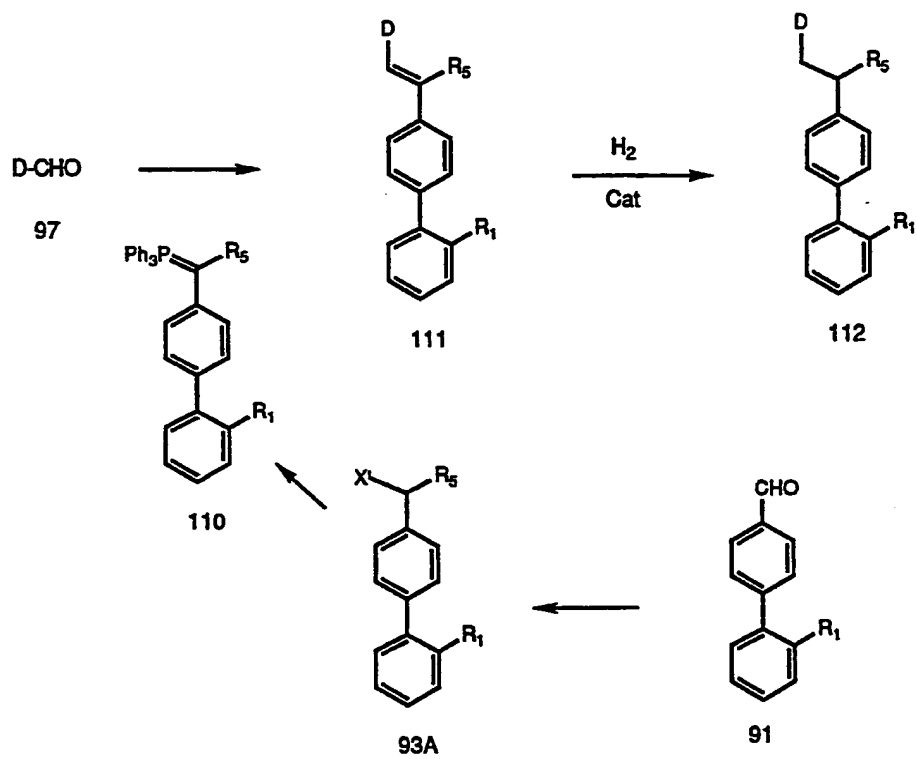
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## SCHEME VIII

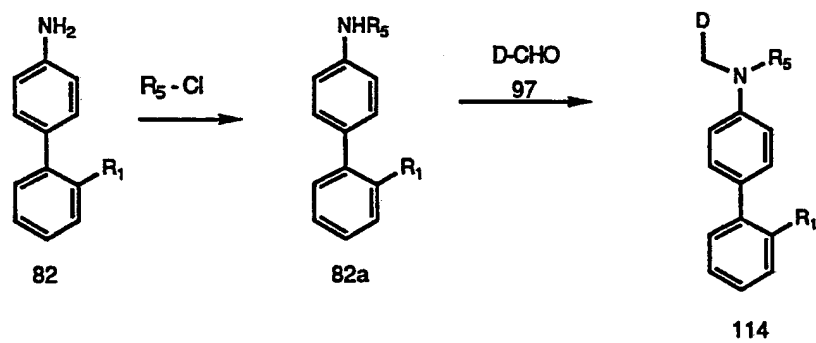


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## SCHEME IX

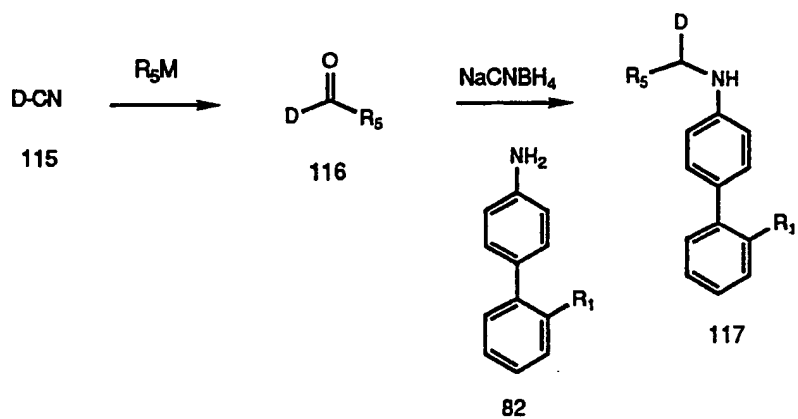


## SCHEME X

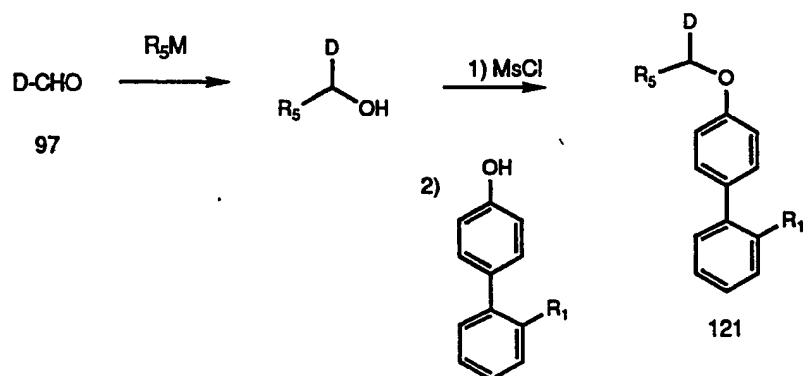


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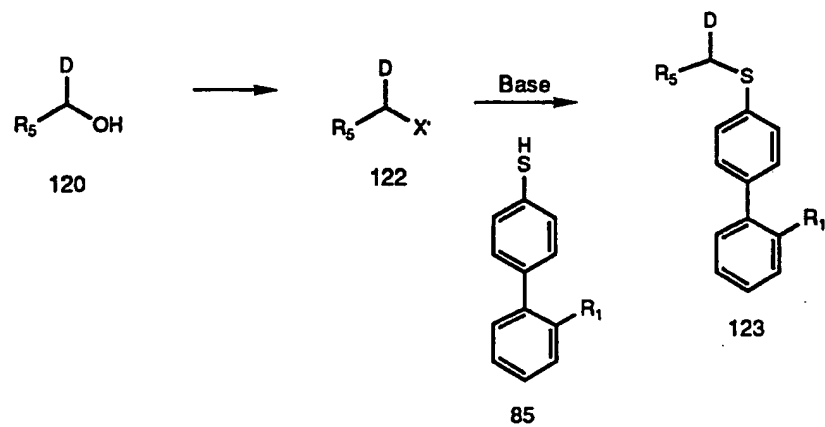
## SCHEME XI



## SCHEME XII

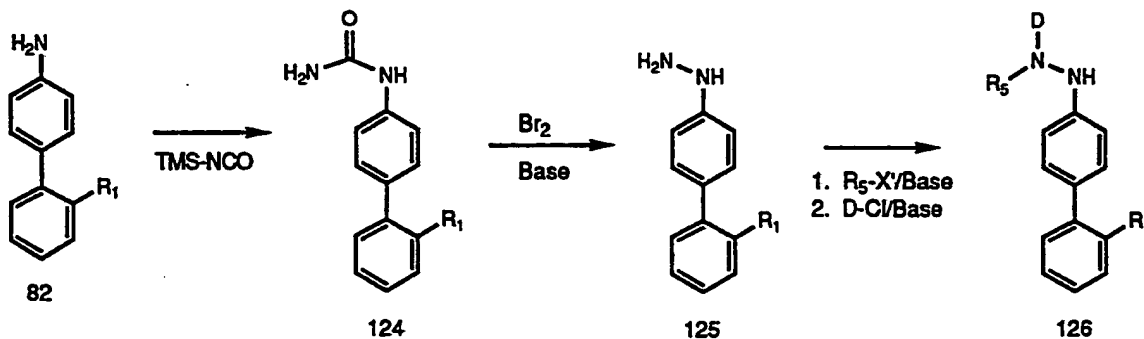


## SCHEME XIII

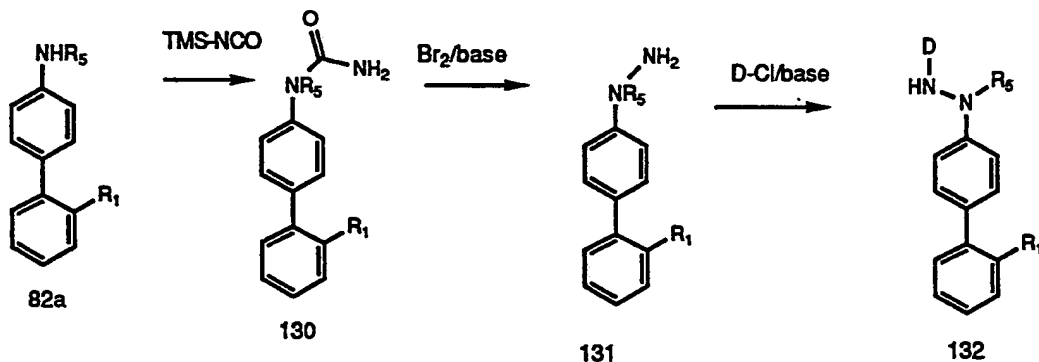


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## SCHEME XIV



## SCHEME XV



Schemes XVI-XXX illustrate methods of preparing compounds of the invention comprising various bicyclic heterocyclic groups (D).

Scheme XVI

Scheme XVI discloses the synthesis of a compound of the invention comprising a substituted pyridopyrimidine (in particular, 4-{N-propyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}-pyrido[3,2-d]pyrimidine-6-carboxylic acid). Broom in J. Org. Chem. **42**, 993 (1977) describes chemistry relating to pyrido[3,2-d]pyrimidines. Treatment of 5-aminouracil with dimethylacetylene

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dicarboxylate affords a Michael adduct of the Formula 200. Cyclization of compound 200 with Dowtherm A provides the trioxo compound of the Formula 201. Exhaustive chlorination of compound 201 with phosphorus oxychloride affords a trichloride of the Formula 202. Treatment of compound 202 with secondary amine 203, prepared as described in Example 2A, affords a compound of the Formula 204. Dechlorination of compound 204 by catalytic hydrogenation with 10% palladium on carbon and triethylamine in ethyl acetate provides a compound of the Formula 205. Detritylation of compound 205 with acid followed by basic hydrolysis of the ester moiety affords a compound of the Formula 206.

#### Scheme XVII

Scheme XVII discloses the synthesis of a compound of the invention comprising a substituted pyridopyrimidine (in particular, 4-{N-propyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}-pyrido[3,2-d]pyrimidine-5-carboxylic acid). Broom in J. Org. Chem. 42, 993 (1977) describes chemistry relating to pyrido[3,2-d]pyrimidines. Exhaustive chlorination of a compound of the Formula 210, prepared according to J. Am. Chem. Soc. 77, 2256 (1953), with phosphorus oxychloride and N,N-diethylaniline affords the trichloride 211. Treatment of compound 211 with secondary amine 203, prepared as described in Example 2A, affords tertiary amine 212. Dechlorination of 212 by catalytic hydrogenation with 10% palladium on carbon in the presence of a base such as triethylamine affords a compound of the Formula 213. Detritylation of 213 under acidic conditions and ester hydrolysis under basic conditions affords a compound of the Formula 214.

#### Scheme XVIII

Scheme XVIII discloses the synthesis of a compound of the invention comprising a substituted quinazoline (in particular, 4-{N-propyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}-quinazoline-5-carboxylic acid. Catalytic hydrogenation of a compound of the Formula 220 with palladium on



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carbon in methanol affords amino compound 221. Treatment of compound 221 with potassium cyanate in refluxing acetic acid affords the known quinazoline 222, J. Het. Chem. 26, 1885 (1989). Exhaustive chlorination of compound 222 with phosphorus oxychloride and N,N-diethylaniline affords dichloride 223. Treatment of compound 223 with secondary amine 203, prepared as described in Example 2A, affords the coupled compound 224. Catalytic hydrogenation of compound 224 with palladium on carbon containing a base such as triethylamine affords the dechlorinated compound 225. Detritylation under acidic conditions followed by base catalyzed ester hydrolysis affords a compound of the Formula 226.

#### Scheme XIX

Scheme XIX discloses the synthesis of a compound of the invention comprising a substituted naphthyridine (in particular, 4-{N-propyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}-1,5-naphthyridine-3-carboxylic acid). Ethyl 4-chloro-1,5-naphthyridine-3-carboxylate 230, prepared by the method of Mendes *et al.*, United States Patent No. 4,996,213, is reacted with amine 203, prepared as described in Example 2A, to give a compound of the Formula 231. Compound 231 is deprotected with formic acid and hydrolyzed with sodium hydroxide to give a compound of the Formula 232.

#### Scheme XX

Scheme XX discloses the synthesis of a compound of the invention comprising a substituted pyridopyrazine (in particular, 8-{N-propyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}pyrido[2,3-b]pyrazine-7-carboxylic acid). Hydroxy ester of the Formula 240, prepared as described by Tanaka and Narita, Yakugaku Zashi 95, 1092 (1975), is chlorinated using a procedure analogous to that described by Meades *et al.*, United State Patent No. 4,996,213, to give a chloro ester of the Formula 241. Compound 241 is reacted with amine 203, prepared as described in Example 2A, to give compound 242 and then deprotected and hydrolyzed to give a compound of the Formula 243.

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### Scheme XXI

Scheme XXI discloses the synthesis of a compound of the invention comprising a substituted pyridopyrimidine (in particular, 2,7-dimethyl-4-{N-propyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}pyrido[4,5-d]pyrimidine). The compound of the Formula 250, prepared by the method of Taylor, J. Am. Chem. Soc. 82, 5711 (1960), is chlorinated by the method of Gupta *et al.*, J. Het. Chem. 12, 1311 (1975), to give a compound of the Formula 251. Reaction of compound 251 with amine 203, prepared as described in Example 2A, affords a compound of the Formula 252 which can be deprotected to give a compound of the Formula 253.

### Scheme XXII

Scheme XXII discloses the synthesis of a compound of the invention comprising a substituted pyridotriazine (in particular, 3,7-dimethyl-5-{N-propyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}pyrido[5,4-e]as-triazine). The compound of the Formula 260, prepared as described by Biffin and Brown, Tetrahedron Lett. 2503 (1968), is reacted with amine 203, prepared as described in Example 2A, by the procedure described by Brown and Sugimoto, Austr. J. Chem. 24, 633 (1971), to give a compound of the Formula 261. Formic acid deprotection gives a compound of the Formula 262.

### Scheme XXIII

Scheme XXIII discloses the synthesis of a compound of the invention comprising a substituted pyridopyrazine (in particular, 2,3-dimethyl-5-{N-propyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}pyrido[3,4-b]pyrazine). The chloro compound of the Formula 270, prepared by the method of Jarn *et al.*, Indian J. Chem. 4, 403 (1966), is reacted with amine 203, prepared as described in Example 2A, using the procedure of Temple *et al.*, J. Het. Chem. 7, 1195 (1970). Catalytic hydrogenation affords a diamine, which is reacted with

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butane-2,3-dione to afford a pyrido[3,4-b]pyrazine of the Formula 272. Deprotection affords a compound of the Formula 273.

#### Scheme XXIV

Scheme XXIV discloses the synthesis of a compound of the invention comprising a substituted pyrimidopyridazine (in particular, 8-{N-propyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}pyrimido[5,4-c]pyridazine). The mercapto compound of the Formula 280, prepared by the method of Nakagomi *et al.*, J. Het. Chem. 5, 523 (1968), is methylated with methyl iodide to give the methylthio compound 281. Reaction of compound 281 with amine 203, prepared as described in Example 2A, affords tertiary amine 282. Deprotection affords a compound of the Formula 283.

#### Scheme XXV

Scheme XXV discloses the synthesis of a compound of the invention comprising a substituted pyrazinopyridazine (in particular, 5-amino-8-{N-propyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}pyrazino[2,3-d]pyridazine). The dichloro compound of the Formula 290, prepared by the method of Patel and Castle, J. Het. Chem. 3, 512 (1966), is reacted with secondary amine 203, prepared as described in Example 2A, to afford tertiary amine 291. Treatment of 291 with ammonia affords amino compound 292. Formic acid deprotection affords a compound of the Formula 293.

#### Scheme XXVI

Scheme XXVI discloses the synthesis of a compound of the invention comprising a substituted naphthyridine (in particular, 2,8-diamino-4-{N-propyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}-1,5-naphthyridine). The trichloro compound of the Formula 300, prepared by the method of Roch *et al.* German Patent 2926804, Chemical Abstracts 95:25109-s, is reacted with secondary amine 203, prepared as described in Example 2A, to give tertiary

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amine 301. Treatment with ammonia affords diamino compound 302. Formic acid deprotection affords a compound of the Formula 303.

#### Scheme XXVII

Scheme XXVII discloses the synthesis of a compound of the invention comprising a substituted naphthyridine (in particular, 7-{N-propyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}-1,6-naphthyridine-8-carboxylic acid). 2-Chloropyridine-3-carboxaldehyde ethylene acetal is treated with sodium hydride and diethylmalonate to give a compound of the Formula 311. Treatment of compound 311 with hydrochloric acid followed by ammonia gives the desired 1,6-naphthyridine 312. Treatment of compound 312 with phosphorus oxychloride gives the 7-chloro compound which is treated with secondary amine 203, prepared as described in Example 2A, under basic conditions to afford tertiary amine 313. Formic acid detritylation followed by sodium hydroxide ester hydrolysis affords a compound of the Formula 314.

#### Scheme XXVIII

Scheme XXVIII discloses the synthesis of a compound of the invention comprising a substituted pyridopyrimidine (in particular, 4-{N-propyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}-pyrido[3,2-d]pyrimidine-2-carboxylic acid). 3-Aminopicolinic acid is treated with urea to give the dihydroxy compound 320. Chlorination converts compound 320 to dichloro compound 321. Treatment of 321 with secondary amine 203, prepared as described in Example 2A, affords tertiary amine 322. Treatment with cyanide anion give the 2-cyano compound 323. Formic acid hydrolysis deprotects the compound and converts the nitrile to a carboxylic acid 324.

#### Scheme XXIX

Scheme XXIX discloses the synthesis of a compound of the invention comprising a substituted naphthyridine (in particular, 8-{N-propyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}-[1,7]naphthyridine-6-carboxylic acid).

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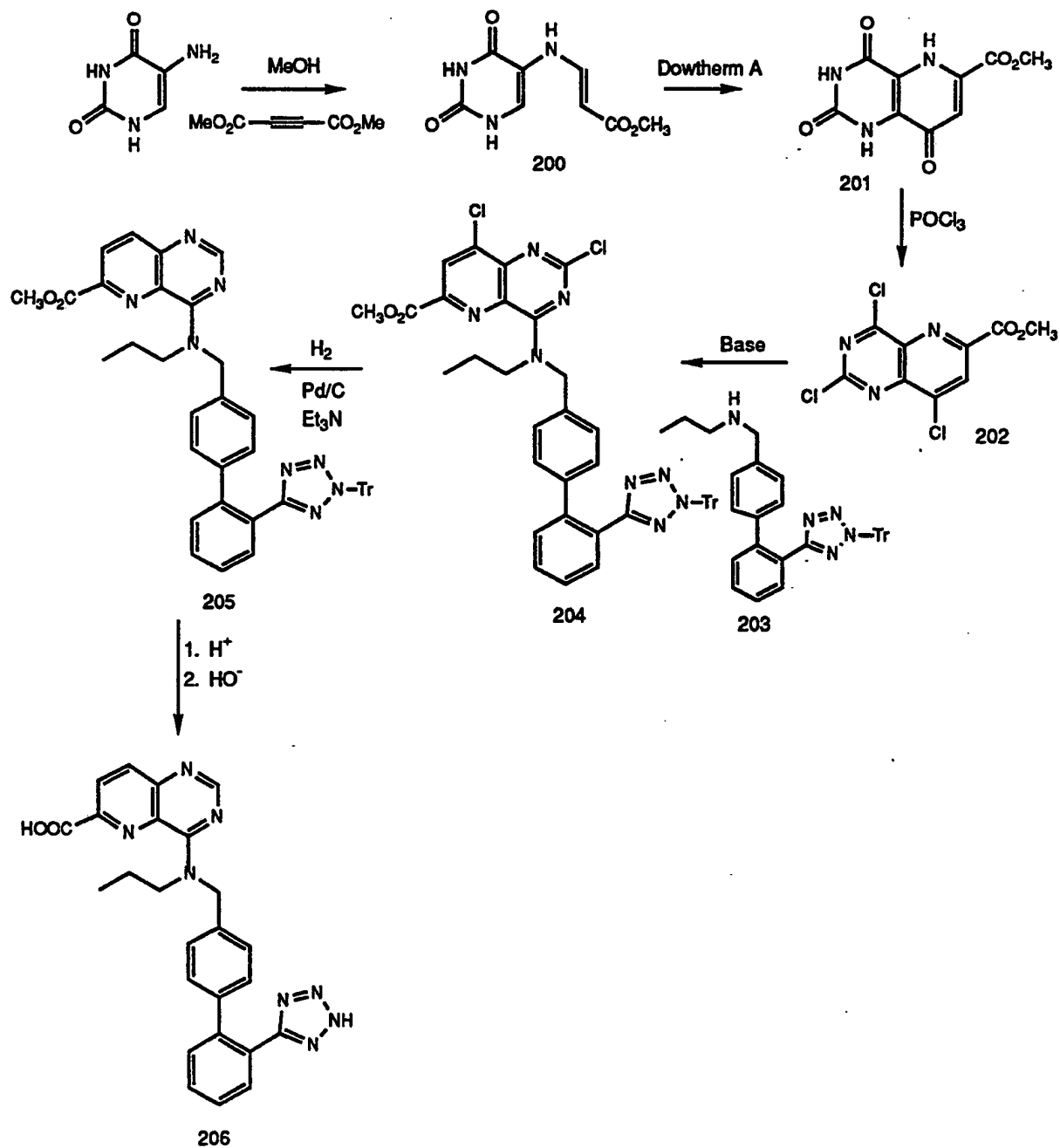
3-Formylpicolinic acid, prepared as described in Gazz. Chim. Ital. 86, 990 (1956) is converted into its ethyl ester 331. The anion of ethyl cyanoacetate is prepared with sodium hydride and reacted with compound 331 to give the [1,7]-naphthyridine compound 332. Alternatively compound 332 is prepared from 2-cyano-3-iodopyridine which is reacted with ethyl 2-ethoxyacrylate with a palladium catalyst and the product thereof cyclized to give compound 332; the analogous reaction was carried out on the benzene analog as described in Heterocycles 27, 453 (1988). Chlorination of 332 with phosphorus oxychloride in analogy to the procedure described in J. Org. Chem. 44, 1887 (1979) for the analogous quinoline gives the chloro compound 333. Treatment of compound 333 with *n*-propylamine gives secondary amine 334. Reaction of compound 334 with bromo compound 335 gives tertiary amine 336. Formic acid detritylation followed by sodium hydroxide ester hydrolysis affords a compound of the Formula 337.

#### Scheme XXX

Scheme XXXIV describes the synthesis of 6-isopropoxy-2-methyl-4-{N-propyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}-1,5-naphthyridine. 2-Chloro-5-nitropyridine is treated with sodium isopropoxide in isopropanol followed by tin (II) chloride dihydrate to give the 5-amino-2-isopropoxy compound of the Formula 340. Treatment of this compound with ethyl acetoacetate followed by acidification and then Dowtherm at 200 °C gives a compound of the Formula 341. Chlorination with phosphorus oxychloride gives the 4-chloro compound 342. The chloro-compound is reacted with secondary amine 203, N-triphenylmethyl-5-[2-(4'-propylaminomethyl-biphenyl)]tetrazole, prepared by the procedure described in Example 72A, under basic conditions to give tertiary amine 343. Formic acid deprotection affords a compound of the Formula 344.

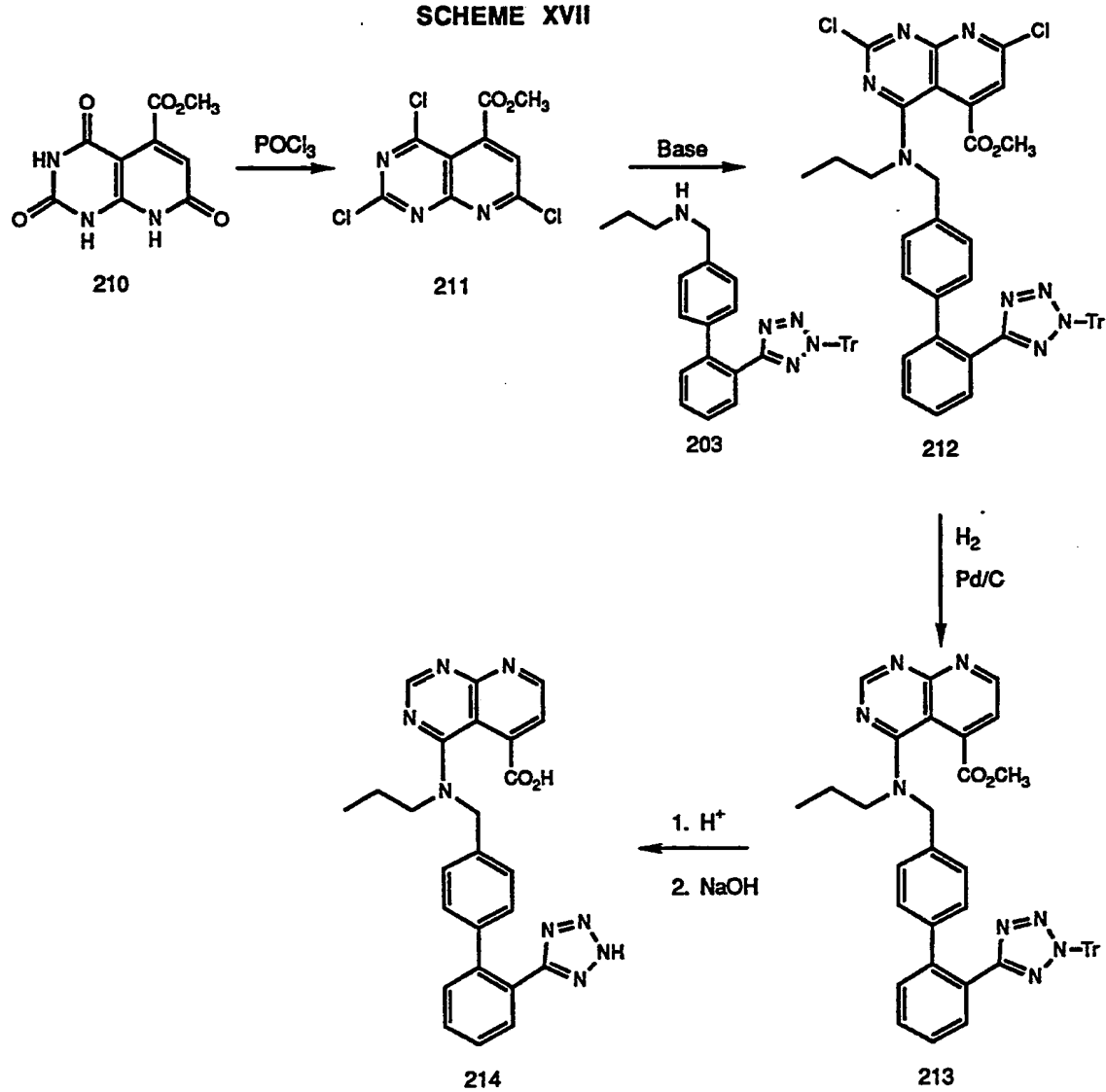
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## SCHEME XVI



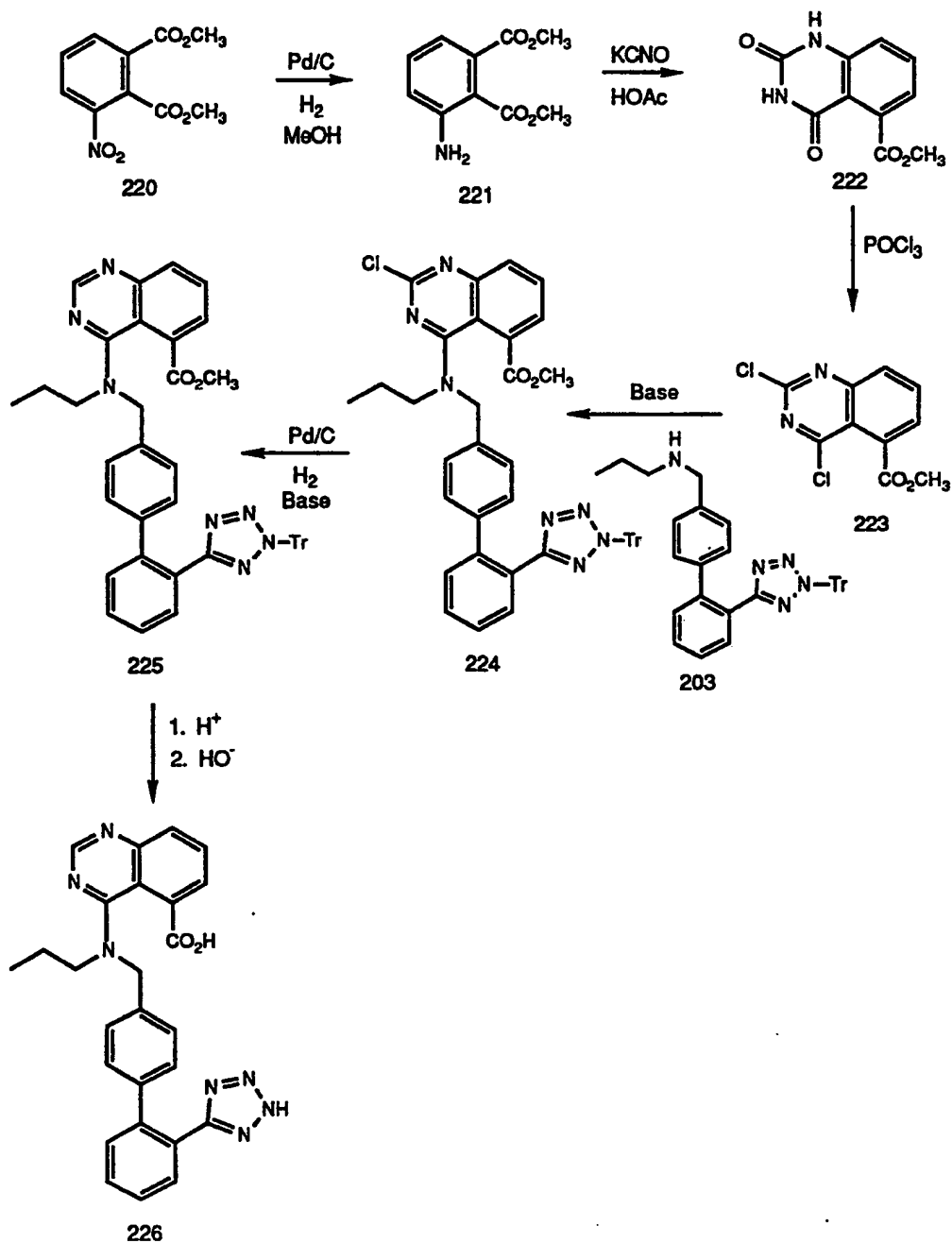
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## SCHEME XVII



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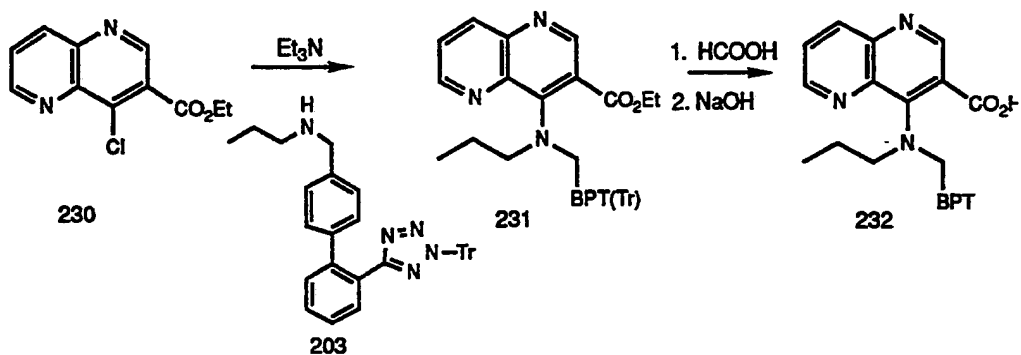
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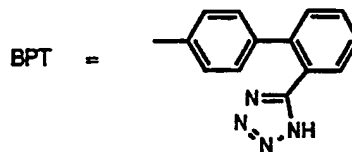
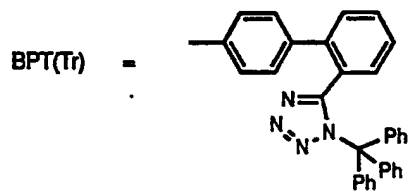
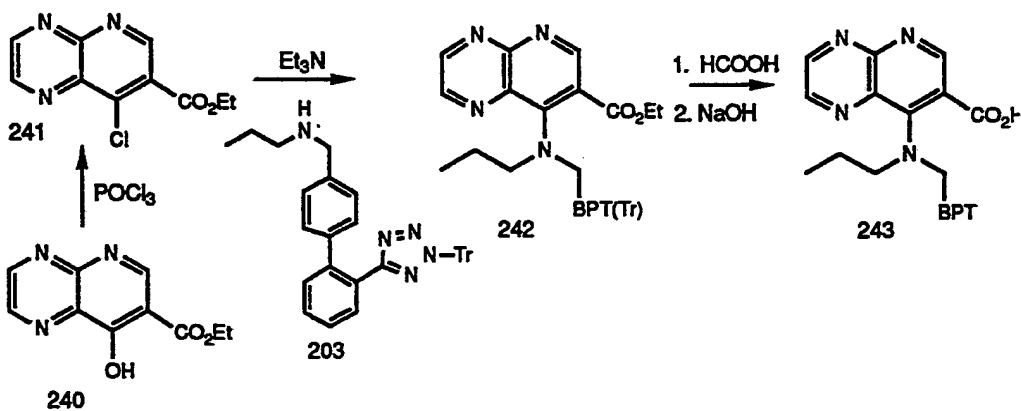


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## SCHEME XIX



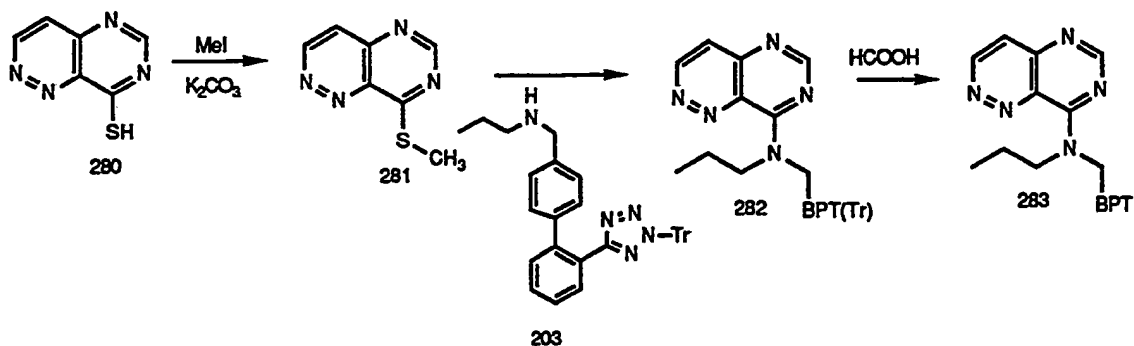
## SCHEME XX



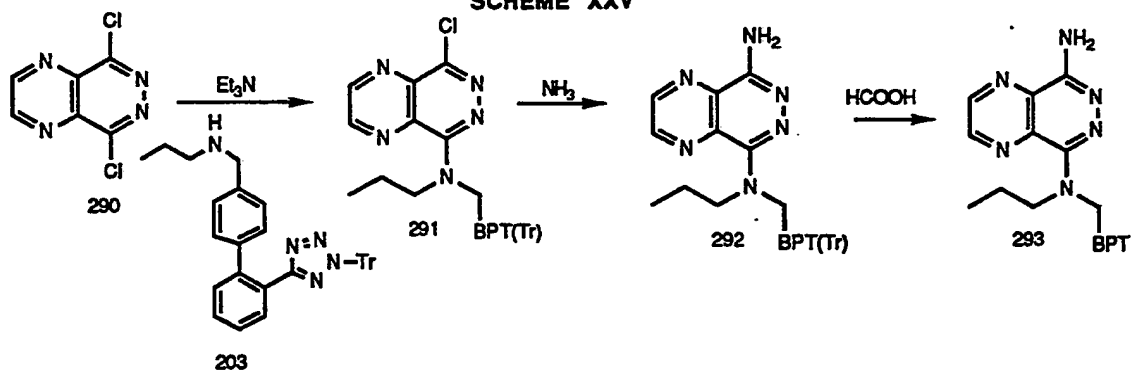


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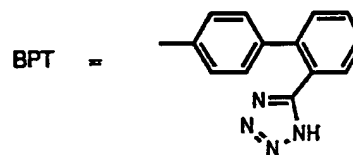
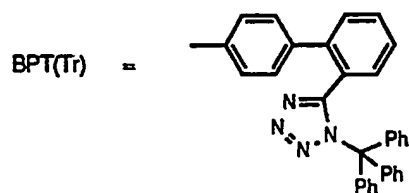
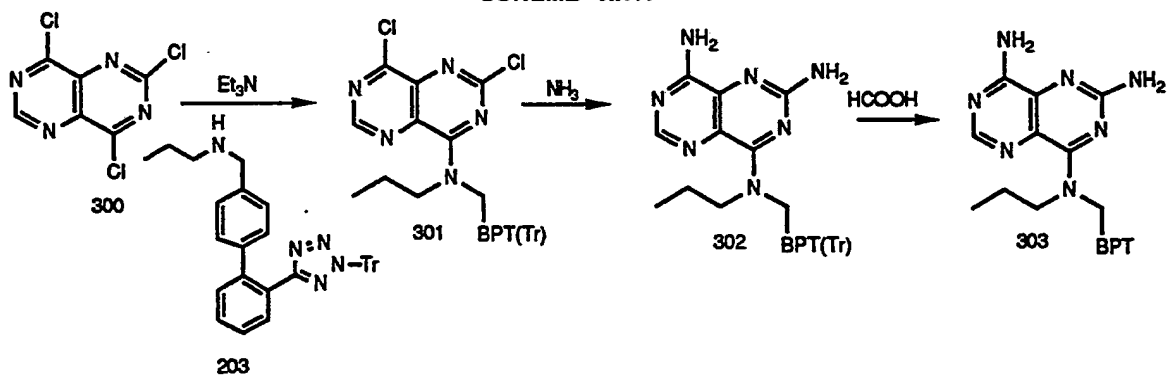
## SCHEME XXIV



## SCHEME XXV

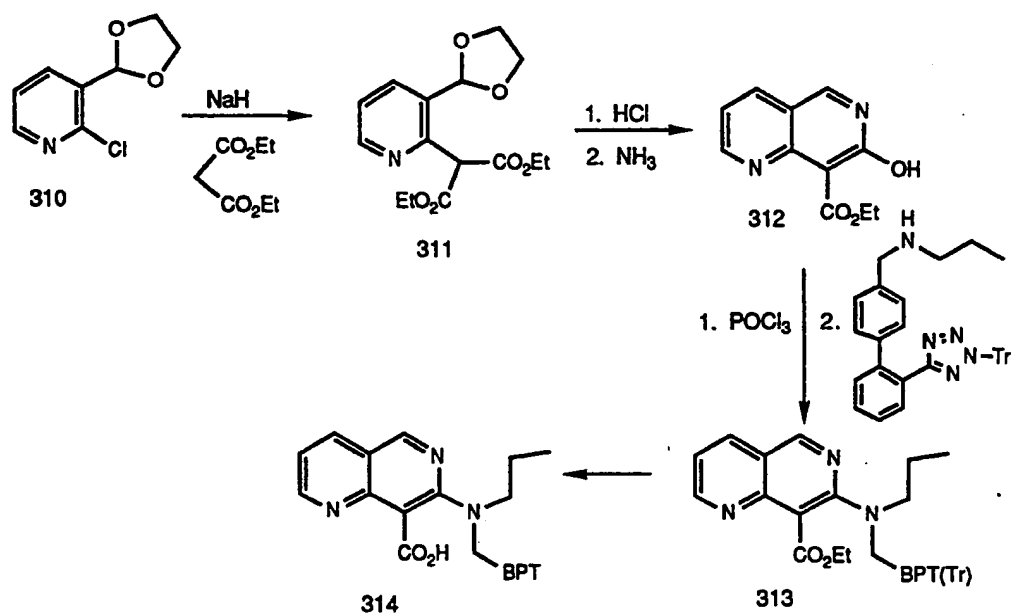


## SCHEME XXVI

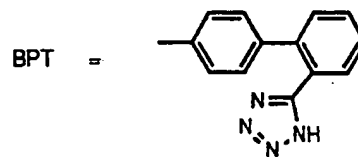
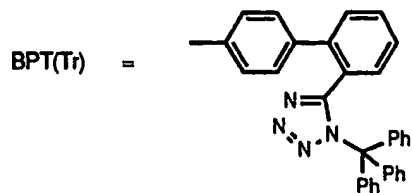
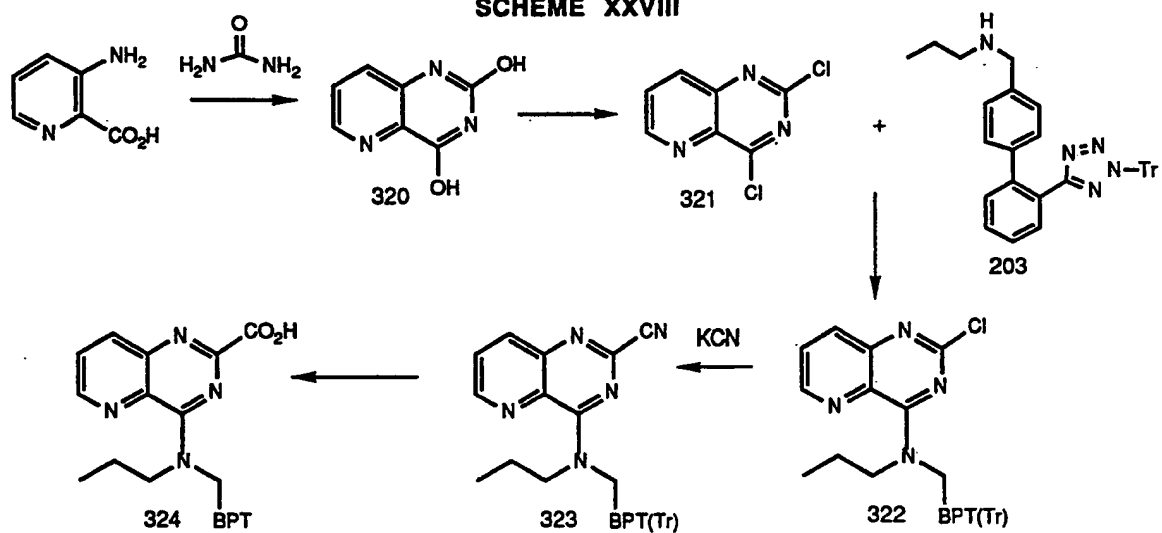


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## SCHEME XXVII

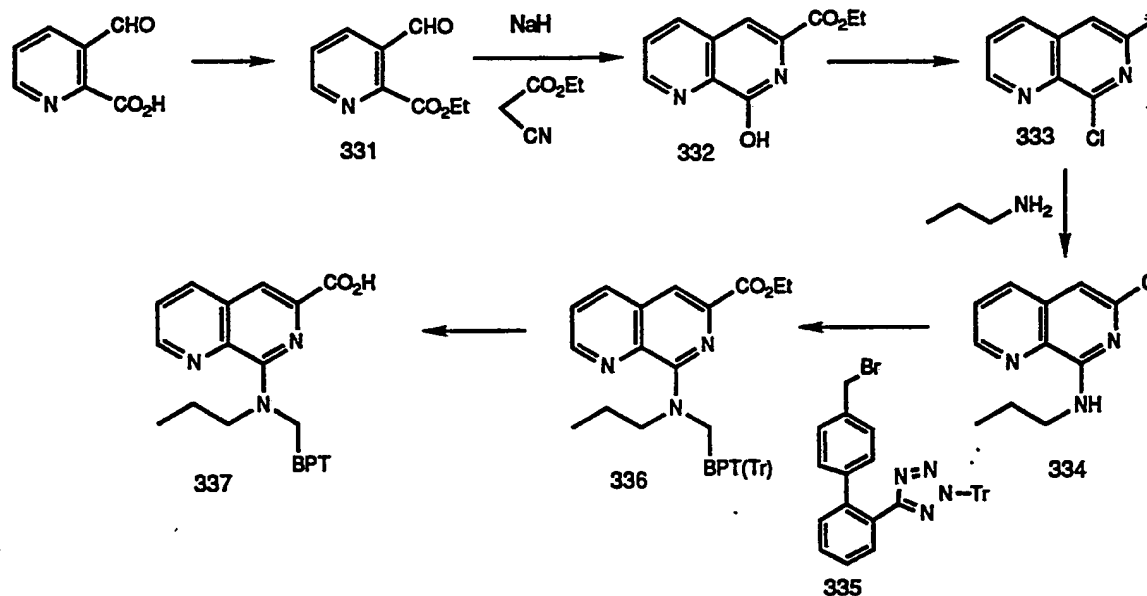


## SCHEME XXVIII

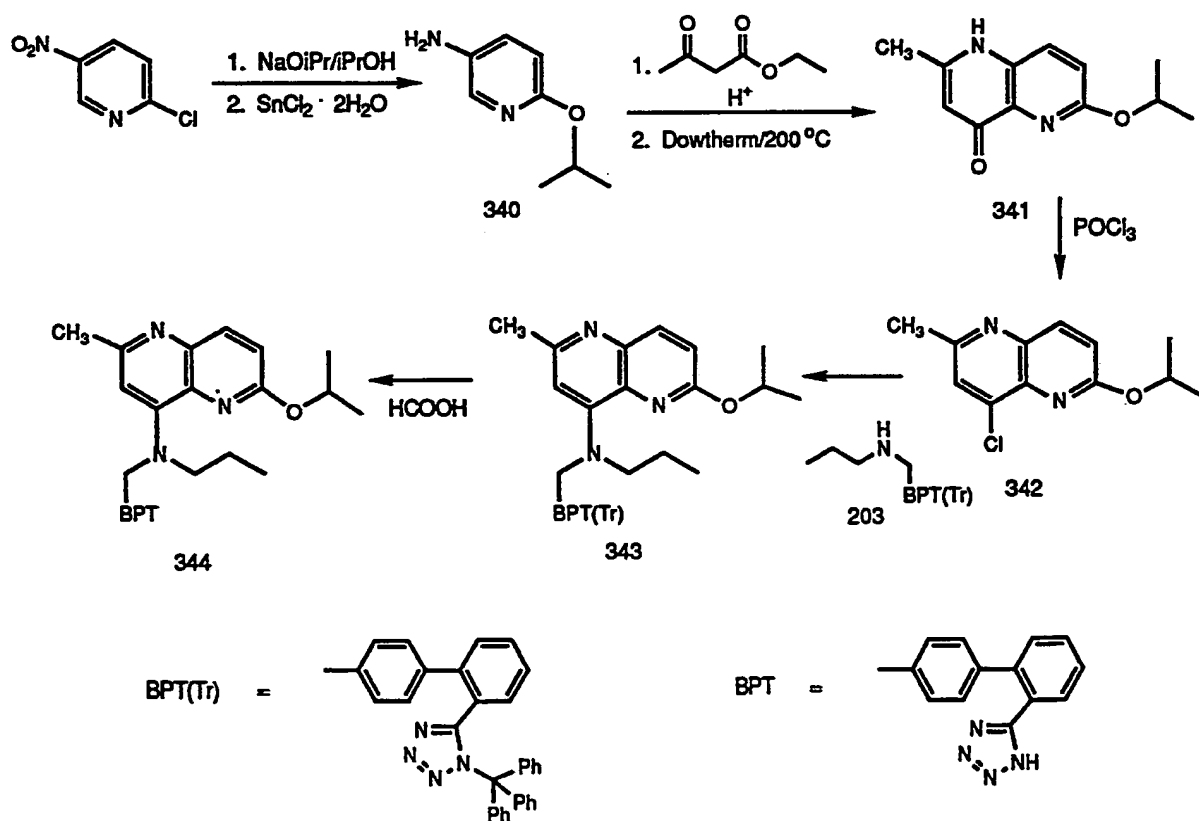


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## SCHEME XXIX

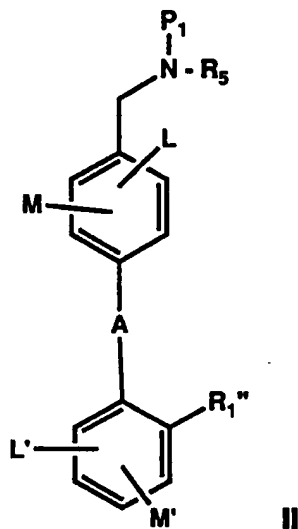


## SCHEME XXX



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Intermediates useful for the preparation of the novel compounds of this invention include a compound of the formula (II):



wherein A, L, L', M, M' and R<sub>5</sub> are defined as above;

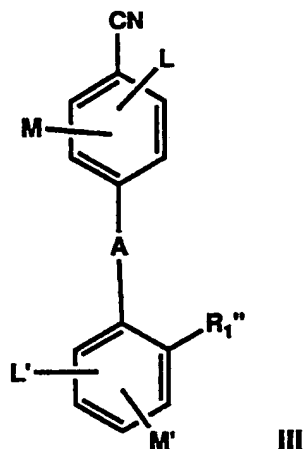
P<sub>1</sub> is hydrogen or an N-protecting group; and

R<sub>1</sub>'' is R<sub>1</sub> as defined above, -NO<sub>2</sub>, -CN or an N-protected tetrazolyl group wherein the tetrazole is N-protected with a trityl group, a t-butyl group, a benzyl group, a benzyloxymethyl group or a methoxymethyl group.

Preferred intermediates of formula II are those wherein A is a bond; L, L', M and M' are hydrogen; and R<sub>1</sub>'' is a tetrazolyl group or an N-protected tetrazolyl group.

Other intermediates useful for the preparation of the novel compounds of this invention include a compound of the formula (III):

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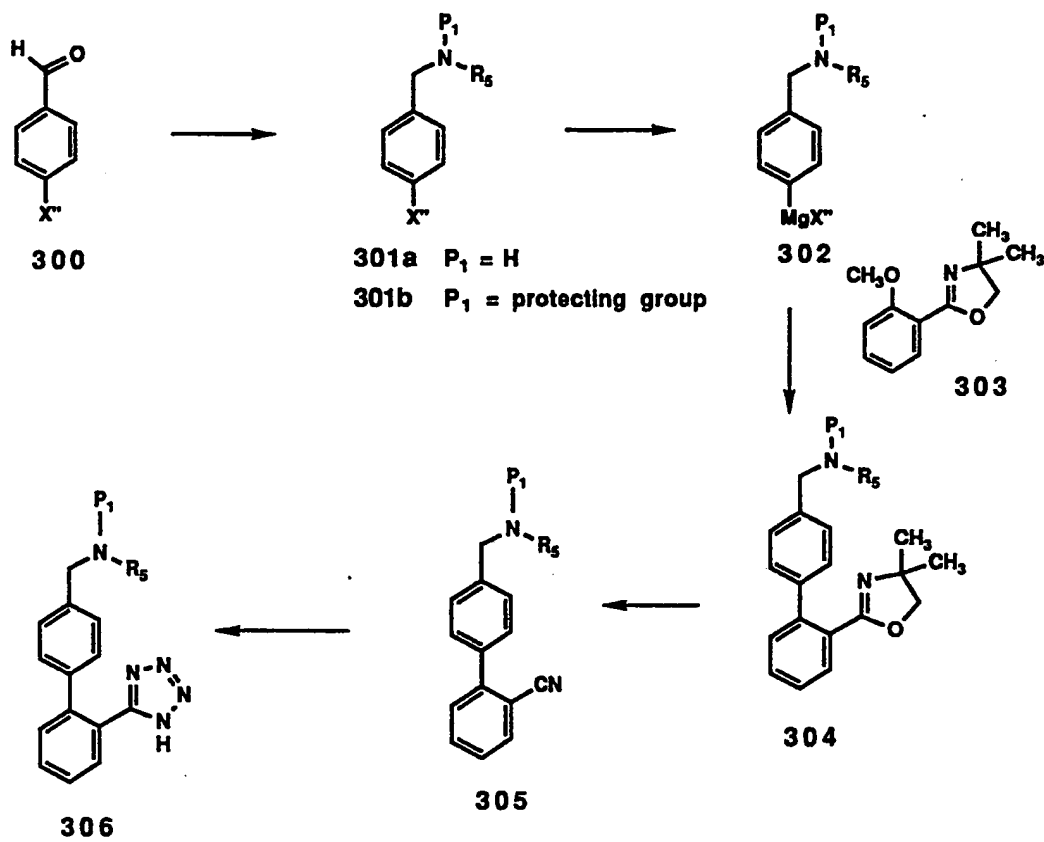
wherein A, L, L', M and M' are defined as above; and R<sub>1</sub><sup>''</sup> is R<sub>1</sub> as defined above, -NO<sub>2</sub>, -CN or an N-protected tetrazolyl group wherein the tetrazole is N-protected with a trityl group, a t-butyl group, a benzyl group, a benzyloxymethyl group or a methoxymethyl group.

Preferred intermediates of formula III are those wherein A is a bond; L, L', M and M' are hydrogen; and R<sub>1</sub><sup>''</sup> is a tetrazolyl group or an N-protected tetrazolyl group.

Intermediates of the formula II wherein A is a covalent bond, L, L', M, and M' are hydrogen and R<sub>1</sub><sup>''</sup> is a tetrazolyl group (i.e., compound 306) can be prepared as illustrated in Scheme XXXI. Aldehyde 300 (X<sup>n</sup> is halogen) can be reductively aminated to provide amine 301a. Protection of the amino group (for example, P<sub>1</sub> = trityl), followed by Grignard formation, provides compound 302. Reaction of 302 with oxazoline 303 provides biphenyl 304. Reaction of biphenyl 304 with POCl<sub>3</sub> provides nitrile 305. Nitrile 305 can then be elaborated to tetrazole 306 (for example, by reaction with sodium azide).

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## SCHEME XXXI





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The foregoing may be better understood from the following examples, which are presented for the purpose of illustration and not intended to limit the scope of the inventive concept.

Example 1

2-[N-Propyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}quinoline-3-carboxylic acid

Example 1A

Ethyl 2-hydroxy-quinoline-3-carboxylate

To O-nitrobenzaldehyde (3.02 g, 20.0 mmol) and diethyl malonate (4.55 mL, 4.80 g, 30 mmol) combined in 7.5 mL of acetic anhydride was added 3.0 g of sodium bicarbonate. The resultant mixture was heated at 80 °C for two hours and then cooled to ambient temperature overnight, during which time the mixture solidified. The reaction mixture was partitioned between ether and water. The organic phase was washed three times with saturated aqueous bicarbonate solution and once with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*.

To the crude product obtained dissolved in 60 mL of ethanol was added 1.0 g of 10% palladium on carbon followed by 15 mL of cyclohexene. The solution was heated at 80 °C for 24 hours and then cooled to ambient temperature. The volatiles were removed *in vacuo* and the residue taken up in 50 mL of ethyl acetate and filtered through a pad of Celite. The solvent was removed *in vacuo* and the residue obtained triturated with ether. Suction filtration and drying afforded the title compound as a white solid (3.06 g, 71% yield). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.34 (t, J = 7Hz, 3H), 1.6 (bs, 1H), 4.46 (q, J = 7Hz, 2H), 7.26 (dt, J = 1Hz, 7Hz, 1H), 7.45 (d, J = 8Hz, 1H), 7.62 (ddd, J =

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1Hz, 7Hz, 8Hz, 1H), 7.78 (dt, J = 7Hz, 1Hz, 1H), 8.57 (s, 1H). MS (DCI/NH<sub>3</sub>) m/e 218 (M+H)<sup>+</sup>.

#### Example 1B

##### Ethyl 2-propylamino-quinoline-3-carboxylate

The compound resulting from Example 1A (0.45 g, 2.1 mmol) was suspended in 2 mL of phosphorus oxychloride and heated at 90 °C for two hours. The solvents were removed *in vacuo* and the residue obtained was neutralized with saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate. The organic phase was dried over sodium sulfate, filtered through Celite and concentrated *in vacuo*. The crude product was combined with 3 mL of ethanol and 2 mL of *n*-propylamine and then heated at 80 °C overnight. The solvents were removed *in vacuo*, and the residue obtained was purified by flash chromatography on silica gel eluting with a gradient of ethyl acetate in hexanes to give 187 mg (34%) of the desired product as well as 171 mg (30%) of the corresponding *n*-propyl amide. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.05 (t, J = 8Hz, 3H), 1.44 (t, J = 7Hz, 3H), 1.74 (sextet, J = 8Hz, 2H), 3.60 (dt, J = 6Hz, 8Hz, 2H), 4.40 (q, J = 7Hz, 2H), 7.17 (dt, J = 1Hz, 7Hz, 1H), 7.57 (dt, J = 1Hz, 8Hz, 1H), 7.63 (t, J = 8Hz, 2H), 7.96 (bs, 1H), 8.63 (s, 1H). MS (DCI/NH<sub>3</sub>) m/e 259 (M+H)<sup>+</sup>.

#### Example 1C

##### Ethyl 2-(N-propyl-N-[(2'-[N-triphenylmethyl-1H-tetrazol-5-yl]biphenyl)-4-yl)methyl]amino)quinolin-3-carboxylate

To the compound resulting from Example 1B (185 mg, 0.72 mmol) dissolved in a mixture of tetrahydrofuran (0.72 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) (0.72 mL) and cooled to 0 °C was added 1 M solution of lithium hexamethyldisilazide in tetrahydrofuran (1 mL) dropwise over 5 minutes. The solution was stirred at 0 °C for 30 minutes and then a solution of 4-bromomethyl-2'-[N-triphenylmethyl-1H-tetrazol-5-yl]biphenyl (1.25 equivalents) in 1.5 mL tetrahydrofuran was added dropwise.

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The solution was allowed to warm to ambient temperature while stirring overnight. The reaction mixture was poured into 1 N aqueous phosphoric acid and extracted with ethyl acetate. The combined organic extracts were washed with saturated sodium bicarbonate and brine, dried over sodium sulfate and concentrated *in vacuo*. The residue obtained was flash chromatographed on silica eluting with a gradient of 10% ethyl acetate in hexanes to give 243 mg (46%) of title product. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 0.75 (t, J = 8Hz, 3H), 1.37 (t, J = 7Hz, 3H), 1.56 (sextet, J = 8Hz, 2H), 3.34 (ddd, J = 1Hz, 7Hz, 8Hz, 2H), 4.46 (q, J = 7Hz, 2H), 4.76 (s, 2H), 6.89 (dd, J = 2Hz, 8Hz, 6H), 7.05 (d, J = 8Hz, 2H), 7.14 (d, J = 8Hz, 2H), 7.25 (m, 10H), 7.38 (ddd, J = 2Hz, 7Hz, 8Hz, 1H), 7.44 (dd, J = 2Hz, 7Hz 1H), 7.48 (dt, J = 2Hz, 7Hz, 1H), 7.59 (dt, J = 1Hz, 8Hz, 1H), 7.67 (s, 1H), 7.69 (d, J = 1Hz, 1H), 7.88 (dd, J = 2Hz, 8Hz, 1H), 8.33 (s, 1H). MS (DCI/NH<sub>3</sub>) m/e 735 (M+H)<sup>+</sup>.

#### Example 1D

#### 2-(N-Propyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino)quinolin-3-carboxylic acid

The compound resulting from Example 1C (240 mg, 0.33 mmol) was dissolved in a mixture of 3 mL of ethanol and 2 mL of tetrahydrofuran. *p*-Toluene sulfonic acid (167 mg) was added, and the resultant solution was stirred at ambient temperature for 8 hours. The reaction was concentrated under reduced pressure, and the residue was taken up in methanol (2 mL). Aqueous sodium hydroxide (2 mL of a 5 N solution) was added. The reaction mixture was stirred overnight. The solvent were removed *in vacuo*; the residue was taken up in water and washed with ethyl acetate. The aqueous phase was acidified with 1 N phosphoric acid and then extracted twice with ethyl acetate. The combined organic extracts were washed with brine, dried over sodium sulfate and concentrated under reduced pressure to provide 153 mg (95%) of the title compound as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 0.99 (t, J = 7Hz, 3H), 1.25 (s, 1H), 1.65 (bd, 2H), 3.71 (bd, 2H), 4.50 (s, 2H), 6.84 (d, J = 8Hz, 2H), 6.93 (d, J = 8Hz, 2H), 7.37 (dd, J = 2Hz, 7Hz, 1H), 7.47 (dt, J =

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2Hz, 7Hz, 1H), 7.54 (dt, J = 2Hz, 8Hz, 1H), 7.79 (t, J = 8Hz, 1H), 7.90 (dt, J = 2Hz, 8Hz, 1H), 7.93 (dd, J = 2Hz, 7Hz, 1H), 8.14 (d, J = 7Hz, 2H), 9.13 (s, 1H). MS (DCI/NH<sub>3</sub>) m/e 465 (M+H)<sup>+</sup>. Anal calcd for C<sub>27</sub>H<sub>24</sub>N<sub>6</sub>O<sub>2</sub>·H<sub>2</sub>O: C, 67.21, H, 5.43, N, 17.42. Found: C, 67.24, H, 5.05, N, 16.60.

### Example 2

#### Ethyl 2-{N-propyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methylamino]-[1,8]naphthyridine-3-carboxylate}

### Example 2A

#### N-Propyl-N-[(2'-[N-triphenylmethyl-1H-tetrazol-5-yl]biphenyl-4-yl)methylamine

N-Triphenylmethyl-5-[2-(4'-bromomethyl-biphenyl)]tetrazole (6.00 g, 10.7 mmol), prepared as described in European Patent Application No. 291969, was dissolved in 55 mL of tetrahydrofuran. *n*-Propylamine (40 mL) was added and the mixture kept at ambient temperature for 2 hours. The solution was concentrated at reduced pressure and the residue obtained taken up in chloroform. The solution was washed with dilute potassium hydroxide solution, dried over potassium carbonate and concentrated under reduced pressure to afford the title compound. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 0.89 (t, J = 7Hz, 3H), 1.50 (sextet, J = 7Hz, 2H), 2.55 (t, J = 7Hz, 2H), 3.68 (s, 2H), 6.85-6.95 (m, 4H), 7.08 (s, 2H), 7.20-7.50 (m, 16H), 7.92 (dd, J = 8Hz, 2Hz, 1H).

### Example 2B

#### Ethyl 2-{N-propyl-N-[(2'-[N-triphenylmethyl-1H-tetrazol-5-yl]biphenyl-4-yl)methylamino]-[1,8]naphthyridine-3-carboxylate}

Ethyl 2-chloro-[1,8]naphthyridine-3-carboxylate, prepared as described in European Patent Application 387582, (1.00 g, 4.23 mmol), the compound resulting from Example 2A (2.60 g, 4.86 mmol) and diisopropyl ethylamine (1.36 g, 10.54 mmol) were dissolved in 5 mL of acetonitrile and refluxed for 3 hours. The solvent was removed under reduced pressure, and the residue obtained was dissolved in chloroform. The chloroform solution was washed

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with sodium bicarbonate solution, dried over sodium sulfate and concentrated under reduced pressure. The residue obtained was chromatographed on silica gel eluting with 8% ethyl acetate in dichloromethane to afford 2.10 g of the title compound as a yellow powder.

#### Example 2C

##### Ethyl 2-{N-propyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}-[1.8]naphthyridine-3-carboxylate

The compound resulting from Example 2B (2.10 g) was dissolved in 17 mL of dichloromethane and 25 mL of 88% formic acid. After stirring for 2 hours at ambient temperature, the mixture was concentrated *in vacuo*. The residue was triturated with a solution (50 mL) of 1:1 formic acid/water and the solid by-product obtained removed by filtration. The filtrate was concentrated under reduced pressure and chased with water. The pH was adjusted to 4.0 using sodium acetate, and the mixture was extracted with chloroform. The combined organic extracts were dried over sodium sulfate and concentrated under reduced pressure. The residue obtained was triturated with ether to give 1.41 g of the title compound as a yellow powder. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 0.80 (t, J = 7Hz, 3H), 1.39 (t, J = 7Hz, 3H), 1.55-1.70 (m, 2H), 3.31 (t, J = 7Hz, 2H), 4.38 (q, J = 7Hz, 2H), 4.74 (s, 2H), 6.95 (d, J = 8Hz, 2H), 7.05 (dd, J = 8Hz, 2H), 7.25 (dd, J = 9Hz, 5Hz, 1H), 7.38 (dd, J = 8Hz, 2Hz, 1H), 8.27 (s, 1H), 8.59 (dd, J = 5Hz, 2Hz, 1H).

#### Example 3

##### 2-{N-Propyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}-[1.8]naphthyridine-3-carboxylic acid

To the compound resulting from Example 2 (1.20 g, 2.43 mmol) was added 0.70 g of sodium hydroxide, 6.6 mL of water and 28 mL of ethanol. The mixture was refluxed for 105 minutes and then cooled in an ice bath. Acetic acid (1 mL) was added and then the solvent was removed under reduced pressure. To the cooled residue was added water, 1 mL of acetic acid and 0.5

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mL of formic acid. The product was removed from solution by filtration and crystallized from acetonitrile to give 0.889 g of the title compound as a yellow solid.  $^1\text{H}$  NMR (DMSO- $d_6$ , 300 MHz)  $\delta$  0.72 (t,  $J$  = 7Hz, 3H), 1.50-1.65 (m, 2H), 3.32 (t,  $J$  = 7Hz, 2H), 4.82 (s, 2H), 6.97 (d,  $J$  = 8Hz, 2H), 7.20 (d,  $J$  = 8Hz, 2H), 7.23 (m, 1H), 7.40-7.60 (m, 4H), 8.21 (dd,  $J$  = 9Hz, 2Hz, 1H), 8.35 (s, 1H), 8.74 (dd,  $J$  = 5Hz, 2Hz, 1H).

#### Example 4

##### 8-{N-Butyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}-[1,7]naphthyridine

#### Example 4A

##### 8-(N-Butylamino)-[1,7]naphthyridine

8-Hydroxy-[1,7]naphthyridine (1.07 g, 7.3 mmol) dissolved in phosphorous oxychloride (30 mL) containing triethylamine (1.12 mL, 8.0 mmol) was heated at 80 °C for 3 hours under nitrogen. The reaction mixture was cooled to ambient temperature and concentrated under reduced pressure. The residue obtained was partitioned between ethyl acetate (50 mL) and water (25 mL). The aqueous layer was extracted with ethyl acetate (2 x 25 mL). The combined organic extracts were dried over magnesium sulfate, filtered and concentrated *in vacuo*.

The crude 8-chloro compound was suspended in 8 mL of ethanol and 4 mL of *n*-butylamine in a sealed tube. The reaction mixture was heated at 110 °C for 5 hours, cooled to ambient temperature, concentrated under reduced pressure and then azeotroped with toluene. The residue obtained was chromatographed on silica gel eluting with 4:1 hexane/ethyl acetate to afford 1.32 g (65%) of the title compound.

#### Example 4B

##### 8-{N-Butyl-N-[(2'-[N-triphenylmethyl]-1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}-[1,7]naphthyridine

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The compound resulting from Example 4A (0.60 g, 3.0 mmol) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) (0.69 mL, 5.7 mmol) were dissolved in tetrahydrofuran (2 mL) and cooled to 0 °C under nitrogen. Lithium bis(trimethylsilyl)amide (3.0 mL of a 1.0M solution in tetrahydrofuran) was added dropwise. After stirring for 6 minutes at 0 °C, N-triphenylmethyl-5-[2-(4'-bromomethyl-biphenyl)]tetrazole, prepared as described in European Patent Application No. 291969, in 5 mL of tetrahydrofuran was added dropwise. The reaction mixture was stirred at ambient temperature for 2 hours and then stored at 0 °C overnight. The reaction mixture was partitioned between ethyl acetate (200 mL) and water (400 mL) containing 25 mL of brine. The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 100 mL). The combined organic extracts were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue obtained was chromatographed on silica gel eluting with 2% ether in toluene. The partially purified product was re-chromatographed on silica gel eluting with 6:1 hexane/ethyl acetate to afford 1.14 g (56%) of the title compound. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 0.88 (t, J = 7.5Hz, 3H), 1.20-1.34 (m, 2H), 1.64-1.76 (m, 2H), 3.83 (t, J = 7.5Hz, 3H), 5.24 (s, 2H), 6.86-6.94 (m, 5H), 7.04 (d, J = 8Hz, 2H), 7.12 (d, J = 8Hz, 2H), 7.17-7.30 (m, 9H), 7.36-7.50 (m, 4H), 7.87 (dd, J = 8Hz, 2Hz, 1H), 7.94 (dd, J = 8Hz, 2Hz, 1H), 8.04 (d, J = 5Hz, 1H), 8.65 (dd, J = 4Hz, 2Hz, 1H). MS (DCI/NH<sub>3</sub>) m/e 678 (M+H)<sup>+</sup>.

#### Example 4C

##### 8-(N-Butyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino)-[1,7]naphthyridine

The compound resulting from Example 4B (1.14 g, 1.68 mmol) in 25 mL of acetic acid, 2 mL of water and 25 mL of tetrahydrofuran was heated at 95 °C for 1 hour. The reaction mixture was concentrated *in vacuo* and chased with toluene (2x). The crude product was chromatographed on silica gel eluting with a gradient of ethanol in methylene chloride to afford 450 mg (60%) of the title compound. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 0.91 (t, J = 7Hz, 3H), 1.25-1.49

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(m, 2H), 1.70-1.82 (m, 2H), 3.98 (t, J = 7Hz, 2H), 5.05 (s, 2H), 6.88 (d, J = 6Hz, 1H), 6.96 (d, J = 8Hz, 2H), 7.06 (d, J = 8Hz, 2H), 7.37 (dd, J = 8Hz, 2Hz, 1H), 7.40-7.54 (m, 3H), 7.78 (d, J = 6Hz, 1H), 7.91-7.97 (m, 2H), 8.03 (bs, 1H), 8.73 (dd, J = 4Hz, 2Hz, 1H). MS (DCI/NH<sub>3</sub>) m/e 436 (M+H)<sup>+</sup>.

#### Example 5

##### 4-{N-Butyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}-pteridine

#### Example 5A

##### N-Butyl-N-[(2'-[N-triphenylmethyl-1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amine

N-Triphenylmethyl-5-[2-(4'-bromomethyl-biphenyl)]tetrazole (6.00 g, 10.7 mmol), prepared as described in European Patent Application No. 291969, was dissolved in 55 mL of tetrahydrofuran. *n*-Butylamine (40 mL) was added and the mixture kept at ambient temperature for 2 hours. The solution was concentrated at reduced pressure and the residue obtained taken up in chloroform. The solution was washed with dilute potassium hydroxide solution, dried over potassium carbonate and concentrated under reduced pressure to afford the title compound. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 0.89 (t, J = 7Hz, 3H), 1.25-1.38 (m, 2H), 1.42-1.52 (m, 2H), 2.60 (t, J = 7Hz, 3H), 3.68 (s, 2H), 6.85-6.95 (m, 4H), 7.08 (s, 2H), 7.20-7.51 (m, 16H), 7.92 (dd, J = 8Hz, 2Hz, 1H).

#### Example 5B

##### 4-{N-Butyl-N-[(2'-[N-triphenylmethyl-1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}-pteridine

4-Hydroxypteridine (2.0 g, 14 mmol), prepared as described in J. Chem. Soc., 2066 (1952), was suspended in 50 mL of phosphorous oxychloride and diisopropylethylamine (2.4 mL, 14 mmol) and heated at 100 °C for 3 hours. The reaction mixture was cooled to ambient temperature, concentrated under reduced pressure, chased with toluene and partitioned between toluene (400 mL), and concentrated sodium bicarbonate solution (50 mL). After filtering the



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emulsion through Celite, the layers were separated. The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure to provide 430 mg (19%) of the crude 4-chloropteridine.

To the 4-chloropteridine (430 mg, 2.6 mmol) and triethylamine (1.1 mL, 7.8 mmol) dissolved in tetrahydrofuran and cooled to 0 °C was added the compound resulting from Example 5A (1.7 g, 3.1 mmol). The reaction mixture was stirred at room temperature for 3 hours and then concentrated under reduced pressure. The residue was partitioned between ethyl acetate (50 mL) and saturated sodium bicarbonate solution (25 mL). The layers were separated and the aqueous layer was extracted with additional ethyl acetate (2 x 25 mL). The combined organic extracts were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue obtained was chromatographed on silica gel eluting with 3:2 ethyl acetate/hexane followed by 18:1:1 ethyl acetate/water/formic acid to provide 1.26 g (72%) of the title compound. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 0.94 (t, J = 7Hz, 3H), 1.27-1.41 (m, 2H), 1.67-1.80 (m, 2H), 3.97 (bm, 2H), 5.66 (bs, 2H), 6.90 (dd, J = 8Hz, 2H, 6H), 7.02-7.12 (m, 5H), 7.19-7.32 (m, 9H), 7.35-7.52 (m, 3H), 7.89-7.94 (m, 1H), 8.74 (bs, 1H), 8.88 (bm, 1H). MS (DCI/NH<sub>3</sub>) m/e 680 (M+H)<sup>+</sup>.

#### Example 5C

##### 4-{N-Butyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}-pteridine

The compound resulting from Example 5B (1.26 g, 1.85 mmol) was dissolved in 88% formic acid (30 mL) and methylene chloride (20 mL). After stirring at ambient temperature overnight, the reaction mixture was concentrated *in vacuo* using a 55 °C water bath. After azeotroping the crude product with toluene, the residue obtained was chromatographed on silica gel eluting with 38:1:1 ethyl acetate/water/formic acid. The partially purified product was rechromatographed on silica gel eluting with a gradient of ethanol in methylene chloride. The purified product was crystallized from acetone/ether to afford 200 mg (25%) of the title compound. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 0.96 (t, J = 7Hz, 3H), 1.14-1.30 (m, 2H), 1.66-1.79 (m, 2H), 3.82

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and 4.07 (bt, 2H), 5.05 and 5.68 (bs, 2H), 6.83 (d, J = 8Hz, 2H), 7.07 (d, J = 8Hz, 2H), 7.28-7.35 (m, 1H), 7.49-7.58 (m, 2H), 7.95-8.01 (m, 1H), 8.28 (bs, 1H), 8.58 (dd, J = 8Hz, 2Hz, 2H). MS (DCI/NH<sub>3</sub>) m/e 438 (M+H)<sup>+</sup>.

#### Example 6

#### 4-{N-Butyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}-pyrido[3,2-d]pyrimidine

#### Example 6A

#### 4-{N-Butyl-N-[(2'-[N-triphenylmethyl-1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}-pyrido[3,2-d]pyrimidine

To a solution of 4-chloropyrido[3,2-d]pyrimidine (0.45 g, 2.7 mmol), prepared by the procedure described in Monatshefte fur Chemie 116, 1309 (1985), and triethylamine (1.1 mL, 8.0 mmol) in 5 mL of anhydrous tetrahydrofuran at 0 °C under nitrogen was added the compound resulting from Example 5A (1.70 g, 3.1 mmol). After stirring for 3 hours at ambient temperature, the solution was concentrated *in vacuo* and the residue partitioned between ethyl acetate (50 mL) and saturated sodium bicarbonate (25 mL). The aqueous layer was extracted with additional ethyl acetate (2 x 25 mL). The combined organic extracts were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue obtained was chromatographed on silica gel eluting with 3:2 ethyl acetate/hexane and then rechromatographed eluting with 18:1:1 ethyl acetate/water/formic acid to afford 1.10 g (62%) of the desired compound. MS (DCI/NH<sub>3</sub>) m/e 679 (M+H)<sup>+</sup>.

#### Example 6B

#### 4-{N-Butyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}-pyrido[3,2-d]pyrimidine

The compound resulting from Example 6A (0.9 g, 1.3 mmol) dissolved in 30 mL of 88% formic acid and 20 mL of methylene chloride was stirred at ambient temperature overnight. After removal of the solvent *in vacuo*, the

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residue was azeotroped with toluene and then chromatographed on silica gel eluting with 38:1:1 ethyl acetate/water/formic acid. The product was crystallized from ethanol/ether and then recrystallized from acetone/ether to afford 120 mg (21%) of the title compound.  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 300 MHz)  $\delta$  0.98 (t,  $J = 7\text{Hz}$ , 3H), 1.34-1.48 (m, 2H), 1.73-1.85 (m, 2H), 4.11 (bt, 2H), 5.56 (bs, 2H), 7.08 (d,  $J = 8\text{Hz}$ , 2H), 7.26 (d,  $J = 8\text{Hz}$ , 1H), 7.49-7.55 (m, 2H), 7.60-7.67 (m, 2H), 7.75 (dd,  $J = 8\text{Hz}$ , 4Hz, 1H), 8.06 (dd,  $J = 8\text{Hz}$ , 2Hz, 1H), 8.49 (s, 1H), 8.75 (bd, 1H). m.p. 127-128 °C. MS ( $\text{DCI}/\text{NH}_3$ )  $m/e$  437 ( $\text{M}+\text{H}$ ) $^+$ .

#### Example 7

##### Methyl 4-{N-butyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}quinazoline-6-carboxylate

#### Example 7A

##### Methyl 4-chloro-quinazoline-6-carboxylate

A suspension of 6-carbomethoxy-4-hydroxyquinazoline (3.5 g, 17 mmol), prepared according to Baker *et al.*, J. Org. Chem. 17, 141 (1952), in phosphorous oxychloride (100 mL) was refluxed for 2 hours. The cooled reaction mixture was concentrated *in vacuo* and redissolved in toluene (200 mL). The organic solution was washed with saturated aqueous sodium bicarbonate and brine, dried over sodium sulfate, decolorized with Norite, filtered and concentrated *in vacuo* to afford the title compound as a solid (1.9 g, 50%).

#### Example 7B

##### Methyl 4-{N-butyl-N-[(2'-[N-triphenylmethyl-1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}quinazoline-6-carboxylate

A solution of the compound resulting from Example 5A (3.9 mmol) in tetrahydrofuran was treated with triethylamine and methyl 4-chloro-quinazoline-6-carboxylate, the compound resulting from Example 7A, (900 mg, 4 mmol). The reaction mixture was stirred for 24 hours at 50 °C. An additional

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portion of methyl 4-chloro-quinazoline-6-carboxylate was added and heating was continued for an additional 48 hours. The volatiles were removed *in vacuo* and the residue obtained dissolved in ethyl acetate (200 mL). The organic solution was washed with saturated aqueous brine, dried over sodium sulfate and sodium carbonate, filtered and concentrated *in vacuo*. The residue obtained was flash chromatographed on silica gel eluting with ethyl acetate in hexanes to afford the title compound as an amorphous solid (2.05 g, 84%).

#### Example 7C

##### Methyl 4-{N-butyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}quinazoline-6-carboxylate

The compound resulting from Example 7B (1.00 g, 1.3 mmol) was dissolved in tetrahydrofuran to which acetic acid and water had been added. The solution was refluxed for 2 hours and then concentrated under reduced pressure. The residue obtained was chromatographed on silica gel eluting with isopropanol in methylene chloride to provide the title compound as a colorless, amorphous solid (400 mg, 62%). MS (DCI/NH<sub>3</sub>) m/e 494 (M+H)<sup>+</sup>.

#### Example 8

##### 4-{N-Butyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}quinazoline-6-carboxylic acid

To the compound resulting from Example 7C (280 mg, 0.55 mmol) dissolved in methanol (10 mL) was added a solution of sodium hydroxide (111 mg, 2.8 mmol) in water (2 mL). After stirring for 16 hours at ambient temperature, the reaction mixture was concentrated under reduced pressure. The residue obtained was dissolved in water (100 mL) and the solution acidified with formic acid. The resulting solid was collected by filtration and recrystallized from methylene chloride and hexane to afford the title compound as an amorphous solid (220 mg, 83%). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 0.92 (t, J = 7.5Hz, 3H), 1.38 (m, 2H), 1.80 (m, 2H), 3.70 (m, 2H), 5.07 (s, 2H), 7.07 (d, J = 7.5Hz, 2H), 7.27 (d, J = 7.5Hz, 2H), 7.50-7.70 (m, 4H), 7.80 (d, J = 7.5Hz,

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1H), 8.22 (dd, J = 7.5Hz, 1Hz, 1H), 8.57 (s, 1H), 8.70 (s, 1H). MS (DCI/NH<sub>3</sub>) m/e 480 (M+H)<sup>+</sup>.

#### Example 9

4-(N-Butyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino)pyrido[3,2-d]pyrimidine-6-carboxylic acid

#### Example 9A

Methyl 2,8-dichloro-4-(N-butyl-N-[(2'-[N-triphenylmethyl-1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino)pyrido[3,2-d]pyrimidine-6-carboxylate

6-Carbomethoxy-2,4,8-trichloropyrido[3,2-d]pyrimidine (1.47 g, 5 mmol), prepared by the procedure described in J. Org. Chem. 44, 433 (1979), was reacted with the compound resulting from Example 5A (5 mmol) by the procedure described in Example 7B. Flash chromatography on silica gel eluting with ethyl acetate/hexane/methylene chloride mixtures provided the title compound as an amorphous solid (2.55 g, 75%). MS (FAB) m/e 805 (M+H)<sup>+</sup>.

#### Example 9B

Methyl 4-(N-butyl-N-[(2'-[N-triphenylmethyl-1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino)pyrido[3,2-d]pyrimidine-6-carboxylate

The product resulting from Example 9A (806 mg, 1 mmol) was mixed with 2 mL of triethylamine and 260 mg of 10% palladium on carbon catalyst in ethyl acetate (120 mL). The mixture was stirred for 4 hours under 1 atmosphere of hydrogen and then additional catalyst (260 mg) was added and stirring continued for 18 hours. A third aliquot (260 mg) was added and stirring continued for an additional 5 hours. The reaction mixture was filtered and the filtrate was washed with saturated brine, dried over sodium sulfate and sodium carbonate and concentrated *in vacuo*. Flash chromatography on silica gel eluting with ethyl acetate in hexane afforded the title compound as an amorphous solid (445 mg, 60%). MS (DCI/NH<sub>3</sub>) m/e 737 (M+H)<sup>+</sup>.

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Example 9C4-{N-Butyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}pyrido[3,2-d]pyrimidine-6-carboxylic acid

The compound resulting from Example 9B (430 mg, 0.583 mmol) was deprotected by the procedure described in Example 7C and hydrolyzed by the procedure described in Example 8 to afford the title compound as an amorphous solid (150 mg, 54%). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 0.88 (t, J = 7.5Hz, 3H), 1.35 (m, 2H), 1.77 (m, 2H), 4.30 (bs, 2H), 5.12 (bs, 2H), 7.04 (d, J = 7Hz, 2H), 7.25 (d, J = 7Hz, 2H), 7.50-7.70 (m, 4H), 8.20 (d, J = 9Hz, 1H), 8.32 (d, J = 9Hz, 1H), 8.53 (s, 1H). MS (DCI/NH<sub>3</sub>) m/e 481 (M+H)<sup>+</sup>.

Example 104-{N-Butyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}-6-methoxyquinazolineExample 10A4-{N-Butyl-N-[(2'-[N-triphenylmethyl-1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}-6-methoxyquinazoline

4-Chloro-6-methoxyquinazoline (0.48 g, 2.5 mmol), prepared by the procedure described in J. Am. Chem. Soc. 68, 1301 (1948), was reacted with the compound resulting from Example 5A (2.2 mmol) by the procedure described in Example 7B. Flash chromatography on silica gel eluting with ethyl acetate in hexane provided the title compound as an amorphous solid (1.05 g, 78%). MS (DCI/NH<sub>3</sub>) m/e 708 (M+H)<sup>+</sup>.

Example 10B4-{N-Butyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}-6-methoxyquinazoline

The compound resulting from Example 10A (610 mg, 0.86 mmol) was deprotected by the procedure described in Example 7C to afford the title compound as an amorphous solid (0.36 g, 90%). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300

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MHz) d 0.92 (t, J = 4.5Hz, 3H), 1.32 (m, 2H), 1.80 (m, 2H), 3.50 (s, 3H), 3.62 (m, 2H), 4.98 (s, 2H), 7.25 (d, J = 6Hz, 2H), 7.35 (d, J = 6Hz, 2H), 7.42 (dd, J = 6Hz, 1Hz, 1H), 7.52-7.73 (m, 5H), 8.52 (s, 1H). MS (DCI/NH<sub>3</sub>) m/e 466 (M+H)<sup>+</sup>.

#### Example 11

#### 4-{N-Pentyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}-6-methyl-quinazoline

#### Example 11A

#### N-Pentyl-N-[(2'-[N-triphenylmethyl-1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amine

The reaction of *n*-pentylamine (6 mL) with N-triphenylmethyl-5-[2-(4'-bromomethyl-biphenyl)]tetrazole, prepared by the procedure described by Aldrich, P. E. *et al.* European Patent Application 291969, (3.00 g, 5.4 mmol) by the procedure described in Example 5A provided the title compound as an amorphous solid (3.00 g, 98%) which was used without further purification.

#### Example 11B

#### 4-{N-Pentyl-N-[(2'-[N-triphenylmethyl-1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}-6-methyl-quinazoline

To the compound resulting from Example 11A (1.77 mmol) dissolved in tetrahydrofuran (15 mL) was added triethylamine (0.5 mL) and 4-chloro-6-methylquinazoline (0.4 g, 2.24 mmol), prepared by the procedure described in J. Chem. Soc., 560 (1962). The reaction mixture was heated at 50 °C for 28 hours and then concentrated *in vacuo*. The work up followed the procedure described in Example 5B. Flash chromatography on silica gel eluting with ethyl acetate in hexane provided the title compound as an amorphous solid (0.5 g, 48%). MS (DCI/NH<sub>3</sub>) m/e 706 (M+H)<sup>+</sup>.

#### Example 11C

#### 4-{N-Pentyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}-6-methyl-quinazoline

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The compound resulting from Example 11B (0.49 g, 0.694 mmol) was deprotected by the procedure described in Example 7C. Purification by flash chromatography on silica gel eluting with ethanol in methylene chloride provided the title compound as an amorphous solid (90 mg, 28%) following recrystallization from methylene chloride and hexane.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  0.90 (t,  $J = 7.5\text{Hz}$ , 3H), 1.20-1.40 (m, 4H), 1.75 (m, 2H), 2.42 (s, 3H), 3.45 (m, 2H), 4.40 (m, 2H), 4.86 (s, 2H), 6.97 (d,  $J = 8\text{Hz}$ , 2H), 7.05 (d,  $J = 8\text{Hz}$ , 2H), 7.40-7.62 (m, 6H), 7.93 (d,  $J = 3\text{Hz}$ , 1H), 7.95 (s, 1H). MS ( $\text{DCI}/\text{NH}_3$ )  $m/e$  464 ( $\text{M}+\text{H}$ ) $^+$ .

#### Example 12

##### 4-{N-Butyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}-6-hydroxy-quinazoline

To the compound resulting from Example 10A (500 mg, 0.706 mmol) dissolved in 50 mL of methylene chloride and cooled to 0 °C was added boron tribromide (1 mL). The reaction mixture was stirred at 0 °C for 30 minutes and at ambient temperature for 30 minutes. The reaction was diluted with 150 mL of methylene chloride and the solution was washed with saturated aqueous ammonium chloride solution. The organic phase was dried over sodium sulfate and the filtered solution was concentrated under reduced pressure and then redissolved in 50 mL of tetrahydrofuran. *p*-Toluene sulfonic acid (400 mg, 2.2 mmol) was added and the reaction mixture was heated at 55 °C for 14 hours at which time potassium carbonate (500 mg) and 1 mL of water were added. The mixture was concentrated under reduced pressure and 100 mL of water was added. Solid sodium hydroxide was added to adjust the pH to 11, and the mixture was extracted with diethyl ether (2 x 100 mL). The aqueous solution was acidified with formic acid and then extracted with ethyl acetate (2 x 100 mL). The combined organic extracts were concentrated under reduced pressure and final traces of formic acid were removed by azeotroping with toluene. Purification by flash chromatography eluting with ethanol and acetic acid in methylene chloride afforded the title compound (32



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mg, 10%) following recrystallization from ethyl acetate in hexane.  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 300 MHz)  $\delta$  0.97 (t,  $J = 9\text{Hz}$ , 3H), 1.40 (m, 2H), 1.85 (m, 2H), 3.80 (m, 2H), 5.17 (s, 2H), 7.15-7.72 (m, 11H), 8.50 (s, 1H). MS (DCI/ $\text{NH}_3$ )  $m/e$  452 ( $\text{M}+\text{H}$ ) $^+$ .

### Example 13

#### 4-{N-Butyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}quinoline-3-carboxylic acid

Ethyl 4-chloroquinoline-3-carboxylate, prepared by the procedure described in J. Med. Chem. 12, 1096 (1969), is reacted with the compound resulting from Example 5A by the procedure described in Example 7B to afford ethyl 4-{N-butyl-N-[(2'-[N-triphenylmethyl-1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}quinoline-3-carboxylate.

The above compound is deprotected by the procedure described in Example 7C and hydrolyzed by the procedure described in Example 8 to afford the title compound.

### Example 14

#### 4-{N-Butyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}-pyrido[2,3-d]pyrimidine-5-carboxylic acid

5-Carbomethoxy-2,4,7-trichloropyrido[2,3-d]pyrimidine, prepared by the procedure described in J. Org. Chem. 42, 993 (1977), is reacted with the compound resulting from Example 5A by the procedure described in Example 7B to afford methyl 4-{N-butyl-N-[(2'-[N-triphenylmethyl-1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}-pyrido[2,3-d]pyrimidine-5-carboxylate.

The above compound is deprotected by the procedure described in Example 7C and hydrolyzed by the procedure described in Example 8 to afford the title compound.

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Example 155-Methoxy-4-{N-butyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}quinazoline

5-Methoxyquinazolin-4-one, prepared by the method described in J. Org. Chem. 17, 141 (1952), is treated with phosphorus oxychloride according to the procedure described in Example 7A to afford 4-chloro-5-methoxyquinazoline.

The above compound is reacted with the compound resulting from Example 5A by the procedure described in Example 7B to afford 5-methoxy-4-{N-butyl-N-[(2'-[N-triphenylmethyl-1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}quinazoline.

The above compound is deblocked using the procedure described in Example 12 to afford the title compound.

Example 16Methyl 4-{N-propyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}quinazoline-5-carboxylateExample 16AMethyl 2,4-dichloroquinazoline-5-carboxylate

Phosphorus oxychloride (25 mL), N,N-diethylaniline (3.5 mL) and 5-carbomethoxy-2,4-dihydroxyquinazoline, prepared as described in J. Het. Chem. 26, 1885 (1989), were refluxed for 6 hours. The mixture was cooled to ambient temperature and concentrated under reduced pressure. The residue obtained was poured into 100 mL of ice-water. After stirring for 10 minutes, the mixture was extracted with ethyl acetate (2 x 100 mL). The combined organic extracts were washed with water until the washes were neutral, dried over sodium sulfate and concentrated *in vacuo*. Ether (150 mL) and silica gel (3 g) were added to the residue and the suspension was filtered. The filtrate was concentrated *in vacuo* and the residue obtained was purified by flash

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chromatography on silica gel to afford the title compound as a light yellow solid (1.2 g, 54%).

**Example 16B**

**Methyl 2-chloro-4-{N-propyl-N-[(2'-[N-triphenylmethyl-1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}quinazoline-5-carboxylate**

The compound resulting from Example 16A (670 mg, 2.6 mmol) and the compound resulting from Example 2A (2.5 mmol) were dissolved in dimethylformamide (5 mL). Triethylamine (1 mL) was added and the reaction was stirred for 30 minutes at ambient temperature. The reaction was worked up by the procedure described in Example 7B and chromatographed on silica gel to afford the title compound as a yellow amorphous solid (1.7 g, 89%).

**Example 16C**

**Methyl 4-{N-propyl-N-[(2'-[N-triphenylmethyl-1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}quinazoline-5-carboxylate**

The compound resulting from Example 16B (3.72 g) was dechlorinated by the procedure described in Example 9B. Chromatography on silica gel eluting with ethyl acetate in hexane afforded the title compound as a yellow amorphous solid (1.89 g, 51%).

**Example 16D**

**Methyl 4-{N-propyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino}quinazoline-5-carboxylate**

The compound resulting from Example 16C is deblocked by the procedure described in Example 7C to afford the title compound.

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Example 175-[2-(4'-N-Propylaminomethyl-biphenyl)]tetrazole hydrochlorideExample 17AN-Benzyloxymethyl-5-(2-bromophenyl)tetrazole

5-(2-Bromophenyl)-[1H]-tetrazole was nitrogen-protected as the benzyloxymethyl (BOM) ether by reaction of a solution of the tetrazole in anhydrous dimethylformamide with technical grade BOM-chloride and anhydrous potassium carbonate. The reaction was complete in less than 60 minutes and the work up involved filtration through Celite and evaporation of the solvent under reduced pressure. The residue obtained was purified by chromatography to afford the title product in 70% yield as an oil which crystallized on standing.

Example 17BN-(4-Bromobenzyl-N-propylamine

To 4-bromobenzaldehyde (100 g, 0.54 mol) and *n*-propylamine (36.3 g, 0.60 mol) in methanol (100 mL) was added 5% platinum on carbon (1.00 g). This mixture was shaken in a Parr hydrogenation reactor overnight to complete formation of the Schiff base. The reaction was then hydrogenated under 4 atmospheres of hydrogen until the theoretical uptake of hydrogen had been consumed. The catalyst was removed by filtration through a 0.45 m nylon frit and washed with methanol. The filtrate was concentrated under reduced pressure and the residue obtained dissolved in ether (500 mL). The ether solution was washed with water (2 x 100 mL), 10% sodium bicarbonate solution (2 x 100 mL), and water (2 x 100 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford the crude title compound (121.34 g). GC-MS showed this material to be 98.5% pure product containing 1.5% of the desbromo compound; the yield is 96.93% based on the GC purity of the product obtained. A sample of this material was purified by bulb-to-bulb distillation (bath temperature

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130-150 °C, 0.18 torr).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  0.92 (t,  $J = 7.4$  Hz, 3H), 1.36 (bs, 1H), 1.53 (tq,  $J_1 = J_2 = 7.4$  Hz, 2H), 2.57 (t,  $J = 7.4$  Hz, 2H), 3.74 (s, 2H), 7.20 (d,  $J = 9$  Hz, 2H), 7.44 (d,  $J = 9$  Hz, 2H). IR (film) 1430, 1060  $\text{cm}^{-1}$ . MS ( $\text{DCI}/\text{NH}_3$ )  $m/e$  228, 230 ( $\text{M}+\text{H}$ ) $^+$ .

#### Example 17C

##### 4-[(N-*tert*-Butyloxycarbonyl-N-propylamino)methyl]phenyl boronic acid

To the compound resulting from Example 17B in methylene chloride at 0 °C was added triethylamine (2 equivalents) and di-*tert*-butyl-dicarbonate (1.05 equivalents). The cooling bath was removed and the mixture allowed to warm to ambient temperature. The solution was diluted with a suitable solvent (ether or hexane), washed with 2 N hydrochloric acid, dried over sodium sulfate and concentrated *in vacuo*. The Boc-protected compound was obtained as a colorless oil in quantitative yield and was used without further purification.

Grignard formation was effected by treatment of magnesium (1.2 equivalents) in tetrahydrofuran with dibromoethane (0.05 equivalents) followed by heating to reflux and then adding a solution of the protected compound from above in tetrahydrofuran. The reaction mixture turned brown and after 4 hours, most of the metal had been consumed. The Grignard reagent was cooled in a dry ice/acetone bath and then transferred *via cannula* into a -70 °C solution of trimethyl borate (2.5 equivalents) (~2 M in tetrahydrofuran). Upon completion of the addition, the cooling bath was removed and the mixture allowed to warm to ambient temperature. The solution was diluted with ether (4 volumes), washed with 3 N hydrochloric acid, ensuring that the aqueous layer was pH 2 or lower. The pH was then adjust to 10 by the addition of 1 N sodium hydroxide and the ether layer was discarded. The aqueous solution was cooled to 0 °C, carefully acidified to pH 2 with 3 N hydrochloric acid and extracted with ether. The combined organic extracts were dried over sodium sulfate and

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concentrated *in vacuo* to about 20% of volume whereupon the boronic acid crystallizes in 36% yield.

Example 17D

N-Benzyloxymethyl-5-{2-[4'-(N-propyl-N-*tert*-butyloxycarbonylamino)methyl-biphenyl]}tetrazole

To palladium tetrakis(triphenylphosphine) (0.05 equivalents) dissolved in toluene was added a solution of the compound resulting from Example 17A (1 equivalent). After 10 minutes, a 2 M aqueous solution of sodium carbonate was added followed by the compound resulting from Example 17C dissolved in the minimum amount of ethanol. The two-phase mixture was rapidly stirred under reflux for 2.5 hours and then cooled to ambient temperature. The solution was diluted with ether and the organic phase was dried over sodium sulfate and concentrated *in vacuo* to afford a brown oil. Filtration through silica gel eluting with 35% ether in hexanes afforded the title compound as a colorless oil (87%).

Example 17E

5-[2-(4'-N-Propylaminomethyl-biphenyl)]tetrazole hydrochloride

To the compound resulting from Example 17D (1.00 g, 1.94 mmol) dissolved in 1 mL of absolute ethanol at ambient temperature was added a solution of anhydrous hydrogen chloride (g) dissolved in ethanol (5 mL, 11.2 M). There was observed an immediate evolution of carbon dioxide which lasted about 90 minutes; also during this time a heavy white precipitate appeared. After 3 hours, the solvent was removed *in vacuo* and the residue triturated with 8 mL of ethyl acetate. The white solid was then dried *in vacuo* at 60 °C to afford the title compound (553 mg, 86%).

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The compounds of the present invention can be used in the form of salts derived from inorganic or organic acids. Pharmaceutically acceptable salts are described in Berge, et al., J. Pharmaceutical Sciences 66 1-19 (1977). These salts include but are not limited to the following: acetate, adipate, alginate, citrate, ascorbate, aspartate, benzoate, benzenesulfonate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptonate, glycerophosphate, hemisulfate, heptonate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, phosphate, 3-phenylpropionate, picrate, pivalate, propionate, stearate, succinate, tartrate, thiocyanate, toluenesulfonate (tosylate), undecanoate and valerate.

Examples of acids which can be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, succinic acid, methanesulfonic acid and citric acid. Other salts include salts with alkali metals or alkaline earth metals, such as sodium, potassium, calcium or magnesium or with organic bases. The salts can be prepared *in situ* during the final isolation and purification of the compounds of formula (I), or separately by reacting the free base function with a suitable acid or by reacting the acidic function with a suitable base.

The compounds of the present invention are useful for blocking the interaction of angiotensin II with angiotensin II receptors and for treating hypertension, edema, renal failure, congestive heart failure, glaucoma, psoriasis, benign prostatic hypertrophy, diabetic nephropathy, diabetic retinopathy, or to prevent atherosclerosis or for treating gastrointestinal disorders associated with enhanced contractility and/or motility of intestinal smooth muscle or for treating contractile disorders of the uterus (including premature contractions, dysmenorrhea and the like) or for treating or preventing

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stroke, cerebral vasospasm or cerebral infarction or for treating CNS disorders (depression, schizophrenia, anxiety or cognitive disorders (Alzheimer's disease, amnesia and senile dementia)) in a human or other mammal. The compounds of the invention are also useful for enhancing intimal wound closure and for reducing luminal thrombogenicity in a human or other mammal.

The ability of the compounds of the invention to block the interaction of angiotensin II with angiotensin II receptors can be demonstrated as described below.

**ANGIOTENSIN II FUNCTIONAL ASSAY: Antagonism of Contraction of Rabbit Aorta**

The protocol reported by A.T Chiu and P.Timmermans (P.C. Wong, *et al. Hypertension*, **13**, 489-497 (1989)) was followed with a few modifications. Female New Zealand White rabbits weighing 2-5 kg were sedated with carbon dioxide and then sacrificed. Main abdominal aortas were removed and placed in Krebs-Henseleit buffer at room temperature.

**Krebs-Henseleit buffer**

<b><u>Buffer Component</u></b>	<b><u>mM Concentration</u></b>
sodium chloride	119.00
potassium chloride	4.70
potassium dihydrogen phosphate	1.20
calcium chloride	2.50
sodium bicarbonate	20.00
magnesium sulfate	1.50
dextrose	11.00
EDTA* disodium calcium salt	0.01

\* EDTA = ethylenediamine tetraacetic acid

The buffer contained no cocaine, propranolol or steroid.

The pH of the buffer was 7.40 at 37°C when saturated with 5% carbon dioxide/95% oxygen.



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The tissues were cleaned of extraneous connective tissue, cut into 3 mm rings, and suspended within a 10 mL tissue bath. All dilutions of peptide preparations were made with 0.3% aqueous BSA. The tissues were primed with 55 mM potassium chloride. Tissues were pre-loaded with 1 g of tension. Tension was recorded on a model 7 Grass polygraph using FT03 transducers. At the end of the equilibrium period, a control cumulative concentration-contractile response curve for angiotensin II (A II:  $1 \times 10^{-10}$  -  $10^{-8}$  M) was obtained. The tissue was washed several times until the baseline was reached. Forty five minutes later, test compound (antagonist) was added and the tissue was incubated for 30 minutes. The concentration-response curve for A II was then repeated in the presence of the test compound. One dose of antagonist was tested per tissue only. For single dose shift experiments a dose of 1 mM of test compound was used, for a full pA<sub>2</sub> experiment multiple doses were used depending upon the potency of the antagonist.

All responses to the control agonist were calculated as a percentage of the maximum response. These points in duplicate were plotted and analyzed according to standard Schild analysis (H.O. Schild, *British J Pharmacology and Chemotherapy*, 2, 189-206 (1947)). The pA<sub>2</sub> values calculated for the compounds of the invention are shown in Table 1. The pA<sub>2</sub> value is the negative logarithm of the [A]<sub>2</sub> value. [A]<sub>2</sub> is the concentration of antagonist which necessitates doubling the agonist concentration in order to achieve the agonist effect which was measured in the absence of antagonist.

The pA<sub>2</sub> value, therefore is a measure of the effectiveness of the compound as an antagonist. The data in Table 1 show that the compounds of the invention are potent antagonists at the angiotensin II receptor.

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Table 1: pA<sub>2</sub> Values from Isolated Rabbit Aorta Assay

<u>Example</u>	<u>pA<sub>2</sub></u>
1	7.77
3	8.47
4	7.04
7	6.97
8	8.02
9	8.19
Sar,-1, Thr-8 All (SARILE)	9.02

The ability of the compounds of the invention to lower blood pressure in vivo in renal artery ligated rats can be demonstrated according to the method disclosed by Cangiano, et al., J. Pharmacol. Exp. Ther. 208 310 (1979)).

The total daily dose of the compounds of this invention administered to a human or other mammal in single or in divided doses can be in amounts, for example, from 0.01 to 25 mg/kg body weight or more usually from 0.1 to 15 mg/kg body weight. Single dose compositions can contain such amounts or submultiples thereof to make up the daily dose. In general, treatment regimens according to the present invention comprise administration to a patient in need of such treatment from about 10 mg to about 1000 mg of the compound(s) of this invention per day in multiple doses or in a single dose of from 10 mg to 1000 mg.

It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgement. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; activity of the specific compound employed; the specific composition

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employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts.

The compounds of the present invention can be administered orally, parenterally, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. Topical administration can also involve the use of transdermal administration such as transdermal patches. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques.

Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs containing inert diluents commonly used in the art such as water. Such compositions can also comprise adjuvants, such as wetting agents; emulsifying and suspending agents; sweetening, flavoring and perfuming agents.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions can be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation can also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

The injectable formulation can be sterilized, for example, by filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the

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form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium just prior to use.

In order to prolong the effect of a drug, it is often desirable to slow the absorption of a drug from subcutaneous or intramuscular injection. The most common way to accomplish this is to inject a suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug becomes dependent on the rate of dissolution of the drug which is, in turn, dependent on the physical state of the drug, for example, the crystal size and the crystalline form. Another approach to delaying absorption of a drug is to administer the drug as a solution or suspension in oil. Injectable depot forms can also be made by forming microcapsule matrices of drugs and biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer and the composition of the polymer, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly-orthoesters and polyanhydrides. The depot injectables can also be made by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter and polyethylene glycol which are solid at ordinary temperature but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

Solid dosage forms for oral administration can include capsules, tablets, pills, powders, prills and granules. In such solid dosage forms the active compound can be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms can also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such as magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms can also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings and other release-controlling coatings.

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Solid compositions of a similar type can also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They can optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferably, in a certain part of the intestinal tract, optionally in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as can be required. Ophthalmic formulations, ear drops, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

The ointments, pastes, creams and gels can contain, in addition to an active compound of this invention, excipients such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to the compounds of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants such as chlorofluorohydrocarbons.

Transdermal patches have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by

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dissolving or dispersing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

Some examples of the materials that can serve as pharmaceutically acceptable carriers are sugars, such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as propylene glycol; polyols such as glycerin, sorbitol, mannitol and polyethylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol and phosphate buffer solutions, as well as other non-toxic compatible substances used in pharmaceutical formulations. Wetting agents, emulsifiers and lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgement of the formulator.

The compounds of the present invention can be administered alone or in combination or in concurrent therapy with other cardiovascular agents independently selected from diuretics, adrenergic blocking agents, vasodilators, calcium channel blockers, angiotensin converting enzyme (ACE) inhibitors, potassium channel activators, antiserotonergic agents, thromboxane synthetase inhibitors, renin inhibitors and other agents useful for treating (in a human or other mammal) hypertension, edema or congestive heart failure.

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Representative diuretics include hydrochlorothiazide, chlorothiazide, acetazolamide, amiloride, bumetanide, benzthiazide, ethacrynic acid, furosemide, indacrinone, metolazone, spironolactone, triamterene, chlorthalidone and the like or a pharmaceutically acceptable salt thereof.

Representative adrenergic blocking agents include phentolamine, phenoxybenzamine, prazosin, terazosin, tolazine, atenolol, metoprolol, nadolol, propranolol, timolol, carteolol and the like or a pharmaceutically acceptable salt thereof.

Representative vasodilators include hydralazine, minoxidil, diazoxide, nitroprusside, flosequinan and the like or a pharmaceutically acceptable salt thereof.

Representative calcium channel blockers include amrinone, bencyclane, diltiazem, fendiline, flunarizine, nicardipine, nimodipine, perhexilene, verapamil, gallopamil, nifedipine and the like or a pharmaceutically acceptable salt thereof.

Representative ACE inhibitors include captopril, enalapril, lisinopril and the like or a pharmaceutically acceptable salt thereof.

Representative potassium channel activators include pinacidil and the like or a pharmaceutically acceptable salt thereof.

Representative antiserotonergic agents include ketanserin and the like or a pharmaceutically acceptable salt thereof.

Representative renin inhibitors include enalkiren, A-72517, PD-134672 or Ro 42-5892 and the like or a pharmaceutically acceptable salt thereof.

Other representative cardiovascular agents include sympatholytic agents such as methyldopa, clonidine, guanabenz, reserpine and the like or a pharmaceutically acceptable salt thereof.

The compound of formula I and the other cardiovascular agent can be administered at the recommended maximum clinical dosage or at lower doses. Dosage levels of the active compounds in the compositions of the invention can be varied so as to obtain a desired therapeutic response depending on the route of administration, severity of the disease and the response of the patient.

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The combination can be administered as separate compositions or as a single dosage form containing both agents.

The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds. Variations and changes which are obvious to one skilled in the art are intended to be within the scope and nature of the invention which are defined in the appended claims.

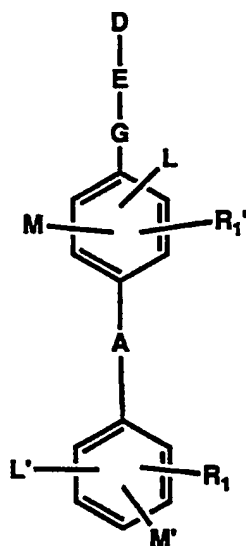


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**CLAIMS**

What is claimed is:

1. A compound of the formula:



wherein

A is

- (i) a covalent bond,
- (ii) -O-,
- (iii) -C(O)-,
- (iv) -CH<sub>2</sub>-,
- (v) -S-, -S(O)- or -S(O)<sub>2</sub>-;

E-G is

- (i) -N(R<sub>5</sub>)-,

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- (ii) -O-,
- (iii) -S-,
- (iv) -N(R<sub>5</sub>)-CH(R<sub>5</sub>)-,
- (v) -O-CH(R<sub>5</sub>)-,
- (vi) -S-CH(R<sub>5</sub>)-,
- (vii) -C(R<sub>5</sub>') (R<sub>5</sub>)-CH(R<sub>5</sub>)-,
- (viii) -CH(R<sub>5</sub>)-C(R<sub>5</sub>') (R<sub>5</sub>)-,
- (ix) -CH(R<sub>5</sub>)-N(R<sub>5</sub>)-,
- (x) -CH(R<sub>5</sub>)-O-,
- (xi) -CH(R<sub>5</sub>)-S-,
- (xii) -N(R<sub>5</sub>)-N(R<sub>5</sub>)-,
- (xiii) -C(R<sub>5</sub>)=C(R<sub>5</sub>)- or
- (xiv) -CH(R<sub>5</sub>)-C(R<sub>5</sub>') (R<sub>5</sub>)-N(R<sub>5</sub>)- wherein at each occurrence R<sub>5</sub> is independently selected from hydrogen, loweralkyl, alkoxy-substituted loweralkyl, halo-substituted loweralkyl, carboxy-substituted loweralkyl, heterocyclic-substituted loweralkyl, alkenyl, alkynyl, cycloalkyl or cycloalkylalkyl and R<sub>5</sub>' is hydrogen, halo, hydroxy, carboxy, alkoxy or thioalkoxy;

L, L', M and M' are independently selected from

- (i) hydrogen,
- (ii) loweralkyl,
- (iii) halo-substituted loweralkyl,
- (iv) halo,
- (v) -CN,
- (vi) -NO<sub>2</sub>,
- (vii) -OH,
- (viii) hydroxy-substituted loweralkyl,
- (ix) alkoxy-substituted loweralkyl,
- (x) -NH<sub>2</sub>,
- (xi) alkylamino,

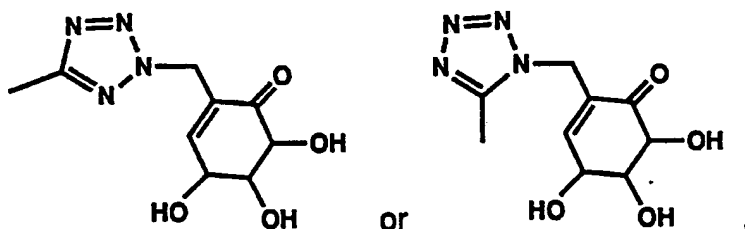
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- (xii) dialkylamino,
- (xiii) -SH,
- (xiv) alkoxy and
- (xv) thioalkoxy;

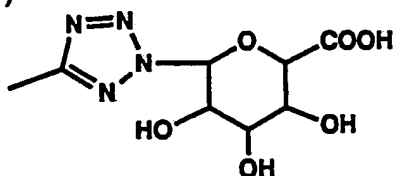
$R_1$  and  $R_1'$  are independently selected from

- (i) tetrazolyl,

(ii)



(iii)



- (iv)  $-NH-C(=N(R_{50a}))(R_{51a})$  wherein  $R_{50a}$  is hydrogen, -CN or  $-NO_2$  and  $R_{51a}$  is hydrogen, loweralkyl, alkylamino, dialkylamino, alkoxy or thioalkoxy,

- (v)  $-NH(R_{51b})$  wherein  $R_{51b}$  is a 5-membered aromatic heterocyclic ring wherein the heterocyclic ring contains 1, 2, 3 or 4 nitrogen atoms or 1 nitrogen atom and 1 oxygen atom or 2 nitrogen atoms and 1 oxygen atom or 1 oxygen atom and 1 sulfur atom and wherein the 5-membered heterocyclic ring is unsubstituted or substituted with a substituent selected from amino, alkylamino, dialkylamino, hydroxy, alkoxy, thioalkoxy, halo, loweralkyl and halo-substituted loweralkyl,

- (vi)  $-COOR_6$  or  $-CH_2COOR_6$  wherein  $R_6$  is hydrogen or a carboxy-

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protecting group or

- (vii) -NHS(O)<sub>2</sub>R<sub>7</sub> or -CH<sub>2</sub>NHS(O)<sub>2</sub>R<sub>7</sub> or -NHC(O)R<sub>7a</sub> or -CH<sub>2</sub>NHC(O)R<sub>7a</sub> wherein R<sub>7</sub> is loweralkyl, halo-substituted loweralkyl or -NR<sub>7b</sub>R<sub>7c</sub> wherein R<sub>7b</sub> and R<sub>7c</sub> are independently selected from hydrogen and loweralkyl and R<sub>7a</sub> is loweralkyl, halo-substituted loweralkyl, amino, alkylamino, dialkylamino or -COOH;
- (viii) -C(O)NR<sub>50</sub>R<sub>51</sub> or -CH<sub>2</sub>C(O)NR<sub>50</sub>R<sub>51</sub> or -NHC(O)NR<sub>50</sub>R<sub>51</sub> or -CH<sub>2</sub>NHC(O)NR<sub>50</sub>R<sub>51</sub> or -NHC(S)NR<sub>50</sub>R<sub>51</sub> or -CH<sub>2</sub>NHC(S)NR<sub>50</sub>R<sub>51</sub> wherein R<sub>50</sub> and R<sub>51</sub> are independently selected from hydrogen, loweralkyl, hydroxy, alkoxy, hydroxy-substituted loweralkyl, alkoxy-substituted loweralkyl, alkoxy-substituted alkoxy and -S(O)<sub>2</sub>R<sub>50a</sub> wherein R<sub>50a</sub> is loweralkyl or aryl, or R<sub>50</sub> and R<sub>51</sub> taken together with the nitrogen atom to which they are attached form a 5- to 7-membered aliphatic heterocycle;
- (ix) -CH<sub>2</sub>OR<sub>52</sub> wherein R<sub>52</sub> is selected from hydrogen, loweralkyl and -C(O)R<sub>53</sub> wherein R<sub>53</sub> is hydrogen, loweralkyl or aryl;
- (x) -CH(OH)R<sub>52a</sub> or -C(O)R<sub>52a</sub> wherein R<sub>52a</sub> is loweralkyl, halo-substituted loweralkyl, -CF<sub>2</sub>COOR<sub>53a</sub> or -CH<sub>2</sub>COOR<sub>53a</sub> wherein R<sub>53a</sub> is hydrogen or a carboxy-protecting group,
- (xii) -CH<sub>2</sub>NR<sub>54</sub>R<sub>55</sub> wherein R<sub>54</sub> is selected from hydrogen, loweralkyl, -C(O)R<sub>56</sub>, -C(O)NR<sub>56</sub>R<sub>57</sub> and -S(O)<sub>2</sub>R<sub>58</sub> wherein R<sub>56</sub> is selected from hydrogen, loweralkyl and aryl and R<sub>58</sub> is selected from lower alkyl and halo-substituted loweralkyl and wherein R<sub>55</sub> and R<sub>57</sub> are independently selected from hydrogen, loweralkyl, hydroxy and alkoxy;
- (xiii) -SO<sub>3</sub>H, -OSO<sub>3</sub>H or -CH<sub>2</sub>SO<sub>3</sub>H,
- (xiv) -OPO<sub>3</sub>H<sub>2</sub>, -PO<sub>3</sub>H<sub>2</sub> or -CH<sub>2</sub>PO<sub>3</sub>H<sub>2</sub>,
- (xv) -SO<sub>2</sub>NR<sub>50</sub>R<sub>51</sub> or -CH<sub>2</sub>SO<sub>2</sub>NR<sub>50</sub>R<sub>51</sub> wherein R<sub>50</sub> and R<sub>51</sub> are defined as above and
- (xvi) -C(O)NHSO<sub>2</sub>R<sub>60</sub>, -C(O)NHC(O)R<sub>60</sub> or -C(O)NHNHSO<sub>2</sub>R<sub>60</sub> wherein R<sub>60</sub> is loweralkyl, halo-substituted loweralkyl or aryl;

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with the proviso that one of  $R_1$  and  $R_1'$  is hydrogen, but  $R_1$  and  $R_1'$  are not both hydrogen;  
and

D is a bicyclic heterocycle comprising a 6-membered ring fused to another 6-membered ring, the bicyclic heterocycle comprising at least one heteroatom selected from N, O and S; each of the 6-membered rings of the bicyclic heterocycle independently comprising 0, 1, 2 or 3 nitrogen atoms or 1 nitrogen atom and 1 oxygen atom or 1 nitrogen atom and 1 sulfur atom or 1 oxygen atom and 1 sulfur atom or 2 oxygen atoms or 2 sulfur atoms or 1 oxygen atom or 1 sulfur atom, the remaining ring atoms being carbon atoms and each of the 6-membered rings of the bicyclic heterocycle comprising 0, 1, 2 or 3 double bonds; the nitrogen atoms of the bicyclic heterocycle can be substituted with a substituent  $R_2$  wherein at each occurrence  $R_2$  is independently selected from hydrogen, loweralkyl, carboxy-substituted loweralkyl or alkoxycarbonyl-substituted loweralkyl; the nitrogen atoms of the bicyclic heterocycle can be oxidized; one or two carbon atoms of the bicyclic heterocycle can be substituted with an oxo (=O) substituent and the sulfur atoms of the bicyclic heterocycle can be substituted with one or two oxo (=O) substituents; the bicyclic heterocycle can be substituted with one, two or three substituents independently selected from  $R_3$  and  $R_4$ ,  $R_3$  being bonded to a carbon atom or a nitrogen atom of the bicyclic heterocycle and  $R_4$  being bonded to a carbon atom or a nitrogen atom of the bicyclic heterocycle, wherein

$R_3$  is

- (i) hydrogen,
- (ii) loweralkyl,
- (iii) halo,
- (iv) halo-substituted loweralkyl,
- (v) thioalkoxy,

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- (vi) alkoxy-substituted loweralkyl,
- (vii) thioalkoxy-substituted loweralkyl,
- (viii) aryl,
- (ix) arylalkyl,
- (x) -NO<sub>2</sub>,
- (xi) -COOR<sub>8</sub> wherein R<sub>8</sub> is hydrogen or a carboxy-protecting group,
- (xii) -OR<sub>9</sub> wherein R<sub>9</sub> is hydrogen, loweralkyl, halo-substituted loweralkyl, aryl, arylalkyl, heterocyclic-substituted loweralkyl or -C(O)R<sub>10</sub> wherein R<sub>10</sub> is loweralkyl, halo-substituted loweralkyl, -PO<sub>3</sub>H<sub>2</sub> or -NR<sub>11</sub>R<sub>12</sub> wherein R<sub>11</sub> and R<sub>12</sub> are independently selected from hydrogen and loweralkyl and
- (xiii) -NR<sub>13</sub>R<sub>14</sub> or -CH<sub>2</sub>NR<sub>13</sub>R<sub>14</sub> wherein R<sub>13</sub> and R<sub>14</sub> are independently selected from (1) hydrogen, (2) lower alkyl, (3) arylalkyl, (4) -C(O)R<sub>15</sub>, (5) -S(O)<sub>2</sub>R<sub>15</sub> wherein R<sub>15</sub> is loweralkyl or halo-substituted loweralkyl and
- (6) -R<sub>16</sub>-R<sub>17</sub> wherein R<sub>16</sub> is alkylene and R<sub>17</sub> is
  - (a) -NR<sub>18</sub>R<sub>19</sub> wherein R<sub>18</sub> and R<sub>19</sub> are independently selected from hydrogen and loweralkyl or
  - (b) unsubstituted or loweralkyl substituted aziridinyl, azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyridinyl or pyrimidinyl, or R<sub>13</sub> and R<sub>14</sub> taken together with the nitrogen atom to which they are attached form a 5- to 7-membered aliphatic heterocycle and

R<sub>4</sub> is

- (i) hydrogen,
- (ii) loweralkyl,
- (iii) halo-substituted loweralkyl,
- (iv) -CN,
- (v) -NO<sub>2</sub>.

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- (vi)  $\text{-NH}_2$ ,
- (vii)  $\text{-NH-C(=N(R}_{25\text{a}}))(\text{R}_{26\text{a}})$  wherein  $\text{R}_{25\text{a}}$  is hydrogen,  $\text{-CN}$  or  $\text{-NO}_2$  and  $\text{R}_{26\text{a}}$  is hydrogen, loweralkyl, alkylamino, dialkylamino, alkoxy or thioalkoxy,
- (viii)  $\text{-NH(R}_{26\text{b}})$  wherein  $\text{R}_{26\text{b}}$  is a 5-membered aromatic heterocyclic ring wherein the heterocyclic ring contains 1, 2, 3 or 4 nitrogen atoms or 1 nitrogen atom and 1 oxygen atom or 2 nitrogen atoms and 1 oxygen atom or 1 oxygen atom and 1 sulfur atom and wherein the 5-membered heterocyclic ring is unsubstituted or substituted with a substituent selected from amino, alkylamino, dialkylamino, hydroxy, alkoxy, thioalkoxy, halo, loweralkyl and halo-substituted loweralkyl,
- (ix)  $\text{-CHO}$  or  $\text{-CH(=N-OH)}$ ,
- (x) tetrazolyl,
- (xi)  $\text{-NHS(O)}_2\text{R}_{20}$  or  $\text{-CH}_2\text{NHS(O)}_2\text{R}_{20}$  or  $\text{-NHC(O)R}_{21}$  or  $\text{-N(OH)C(O)R}_{21}$  or  $\text{-CH}_2\text{NHC(O)R}_{21}$  or  $\text{-CH}_2\text{N(OH)C(O)R}_{21}$  wherein  $\text{R}_{20}$  is loweralkyl, halo-substituted loweralkyl or  $\text{-NR}_{27\text{a}}\text{R}_{27\text{b}}$  wherein  $\text{R}_{27\text{a}}$  and  $\text{R}_{27\text{b}}$  are independently selected from hydrogen,  $\text{-OH}$  and loweralkyl and  $\text{R}_{21}$  is loweralkyl, halo-substituted loweralkyl, amino, alkylamino, dialkylamino or  $\text{-COOH}$ ,
- (xii)  $\text{-CH(OH)R}_{22}$  or  $\text{-C(O)R}_{22}$  wherein  $\text{R}_{22}$  is loweralkyl, halo-substituted loweralkyl,  $\text{-CF}_2\text{COOR}_{23}$  or  $\text{-CH}_2\text{COOR}_{23}$  wherein  $\text{R}_{23}$  is hydrogen or a carboxy-protecting group,
- (xiii)  $\text{-COOR}_{24}$  or  $\text{-CH}_2\text{COOR}_{24}$  wherein  $\text{R}_{24}$  is hydrogen or a carboxy-protecting group,
- (xiv)  $\text{-C(O)NR}_{25}\text{R}_{26}$  or  $\text{-CH}_2\text{C(O)NR}_{25}\text{R}_{26}$  or  $\text{-NHC(O)NR}_{25}\text{R}_{26}$  or  $\text{-CH}_2\text{NHC(O)NR}_{25}\text{R}_{26}$  or  $\text{-NHC(S)NR}_{25}\text{R}_{26}$  or  $\text{-CH}_2\text{NHC(S)NR}_{25}\text{R}_{26}$  wherein  $\text{R}_{25}$  and  $\text{R}_{26}$  are independently selected from hydrogen, loweralkyl, hydroxy, alkoxy, hydroxy-substituted loweralkyl, alkoxy-substituted loweralkyl, alkoxy-substituted alkoxy and  $\text{-S(O)}_2\text{R}_{28\text{a}}$  wherein  $\text{R}_{28\text{a}}$  is loweralkyl or aryl, or  $\text{R}_{25}$  and

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R<sub>26</sub> taken together with the nitrogen atom to which they are attached form a 5- to 7- membered aliphatic heterocycle;

- (xv) -CH<sub>2</sub>OR<sub>27</sub> wherein R<sub>27</sub> is selected from hydrogen, loweralkyl and -C(O)R<sub>28</sub> wherein R<sub>28</sub> is hydrogen, loweralkyl or aryl;
- (xvi) -CH<sub>2</sub>NR<sub>29</sub>R<sub>30</sub> wherein R<sub>29</sub> is selected from hydrogen, loweralkyl, -C(O)R<sub>31</sub>, -C(O)NR<sub>31</sub>R<sub>32</sub> and -S(O)<sub>2</sub>R<sub>33</sub> wherein R<sub>31</sub> is selected from hydrogen, loweralkyl and aryl and R<sub>33</sub> is selected from loweralkyl and halo-substituted loweralkyl and wherein R<sub>30</sub> and R<sub>32</sub> are independently selected from hydrogen, loweralkyl, hydroxy and alkoxy;
- (xvii) -SO<sub>3</sub>H, -OSO<sub>3</sub>H or -CH<sub>2</sub>SO<sub>3</sub>H,
- (xviii) -OPO<sub>3</sub>H, -PO<sub>3</sub>H<sub>2</sub> or -CH<sub>2</sub>PO<sub>3</sub>H<sub>2</sub>,
- (xix) -SO<sub>2</sub>NR<sub>25</sub>R<sub>26</sub> or -CH<sub>2</sub>SO<sub>2</sub>NR<sub>25</sub>R<sub>26</sub> wherein R<sub>25</sub> and R<sub>26</sub> are defined as above and
- (xx) -C(O)NHSO<sub>2</sub>R<sub>59</sub>, -C(O)NHC(O)R<sub>59</sub> or -C(O)NHNHSO<sub>2</sub>R<sub>59</sub> wherein R<sub>59</sub> is loweralkyl, halo-substituted loweralkyl or aryl;

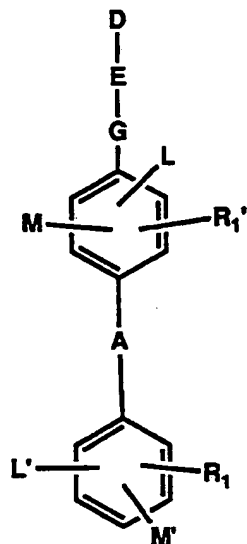
or a pharmaceutically acceptable salt or prodrug thereof.

2. The compound of Claim 1 wherein A is a covalent bond, L, L', M, M' and R<sub>1</sub>' are hydrogen, -G-E- is -CH<sub>2</sub>-N(R<sub>5</sub>)- and D is a substituted naphthyridinyl group, a substituted pyridopyrimidinyl group or a substituted quinazolinyl group.



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3. A compound of the formula:



wherein

A is

- (i) a covalent bond,
- (ii) -O-,
- (iii) -C(O)-,
- (iv) -CH<sub>2</sub>-,
- (v) -S-, -S(O)- or -S(O)<sub>2</sub>-;

E-G is

- (i) -N(R<sub>5</sub>)-,
- (ii) -O-,
- (iii) -S-,
- (iv) -N(R<sub>5</sub>)-CH(R<sub>5</sub>)-,
- (v) -O-CH(R<sub>5</sub>)-,
- (vi) -S-CH(R<sub>5</sub>)-,

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- (vii)  $-\text{C}(\text{R}_5')(\text{R}_5)-\text{CH}(\text{R}_5)-$ ,
- (viii)  $-\text{CH}(\text{R}_5)-\text{C}(\text{R}_5')(\text{R}_5)-$ ,
- (ix)  $-\text{CH}(\text{R}_5)-\text{N}(\text{R}_5)-$ ,
- (x)  $-\text{CH}(\text{R}_5)-\text{O}-$ ,
- (xi)  $-\text{CH}(\text{R}_5)-\text{S}-$ ,
- (xii)  $-\text{N}(\text{R}_5)-\text{N}(\text{R}_5)-$ ,
- (xiii)  $-\text{C}(\text{R}_5)=\text{C}(\text{R}_5)-$  or
- (xiv)  $-\text{CH}(\text{R}_5)-\text{C}(\text{R}_5')(\text{R}_5)-\text{N}(\text{R}_5)-$  wherein at each occurrence  $\text{R}_5$  is independently selected from hydrogen, loweralkyl, alkoxy-substituted loweralkyl, halo-substituted loweralkyl, carboxy-substituted loweralkyl, heterocyclic-substituted loweralkyl, alkenyl, alkynyl, cycloalkyl or cycloalkylalkyl and  $\text{R}_5'$  is hydrogen, halo, hydroxy, carboxy, alkoxy or thioalkoxy;

L, L', M and M' are independently selected from

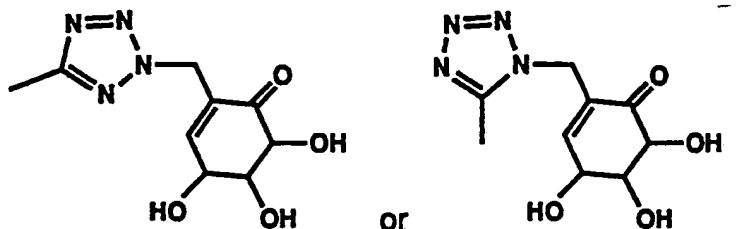
- (i) hydrogen,
- (ii) loweralkyl,
- (iii) halo-substituted loweralkyl,
- (iv) halo,
- (v)  $-\text{CN}$ ,
- (vi)  $-\text{NO}_2$ ,
- (vii)  $-\text{OH}$ ,
- (viii) hydroxy-substituted loweralkyl,
- (ix) alkoxy-substituted loweralkyl,
- (x)  $-\text{NH}_2$ ,
- (xi) alkylamino,
- (xii) dialkylamino,
- (xiii)  $-\text{SH}$ ,
- (xiv) alkoxy and
- (xv) thioalkoxy;

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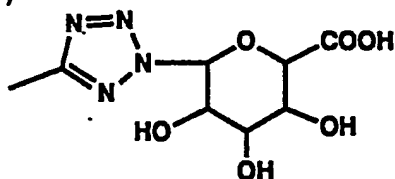
$R_1$  and  $R_1'$  are independently selected from

(i) tetrazolyl,

(ii)



(iii)



(iv)  $-NH-C(=N(R_{50a}))(R_{51a})$  wherein  $R_{50a}$  is hydrogen,  $-CN$  or  $-NO_2$  and  $R_{51a}$  is hydrogen, loweralkyl, alkylamino, dialkylamino, alkoxy or thioalkoxy,

(v)  $-NH(R_{51b})$  wherein  $R_{51b}$  is a 5-membered aromatic heterocyclic ring wherein the heterocyclic ring contains 1, 2, 3 or 4 nitrogen atoms or 1 nitrogen atom and 1 oxygen atom or 2 nitrogen atoms and 1 oxygen atom or 1 oxygen atom and 1 sulfur atom and wherein the 5-membered heterocyclic ring is unsubstituted or substituted with a substituent selected from amino, alkylamino, dialkylamino, hydroxy, alkoxy, thioalkoxy, halo, loweralkyl and halo-substituted loweralkyl,

(vi)  $-COOR_6$  or  $-CH_2COOR_6$  wherein  $R_6$  is hydrogen or a carboxy-protecting group or

(vii)  $-NHS(O)_2R_7$  or  $-CH_2NHS(O)_2R_7$  or  $-NHC(O)R_{7a}$  or  $-CH_2NHC(O)R_{7a}$  wherein  $R_7$  is loweralkyl, halo-substituted loweralkyl or  $-NR_{7b}R_{7c}$  wherein  $R_{7b}$  and  $R_{7c}$  are independently selected from hydrogen and loweralkyl and  $R_{7a}$  is loweralkyl, halo-

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substituted loweralkyl, amino, alkylamino, dialkylamino or -COOH;

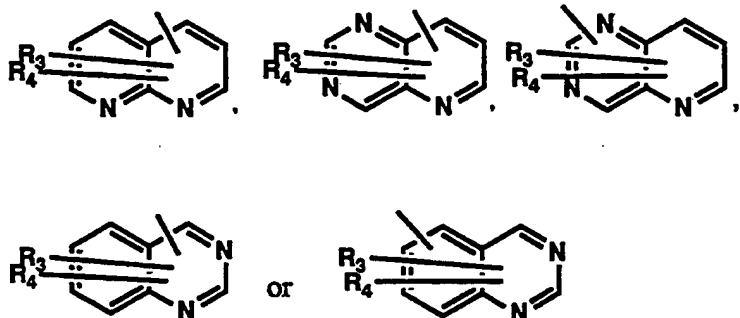
- (viii) -C(O)NR<sub>50</sub>R<sub>51</sub> or -CH<sub>2</sub>C(O)NR<sub>50</sub>R<sub>51</sub> or -NHC(O)NR<sub>50</sub>R<sub>51</sub> or -CH<sub>2</sub>NHC(O)NR<sub>50</sub>R<sub>51</sub> or -NHC(S)NR<sub>50</sub>R<sub>51</sub> or -CH<sub>2</sub>NHC(S)NR<sub>50</sub>R<sub>51</sub> wherein R<sub>50</sub> and R<sub>51</sub> are independently selected from hydrogen, loweralkyl, hydroxy, alkoxy, hydroxy-substituted loweralkyl, alkoxy-substituted loweralkyl, alkoxy-substituted alkoxy and -S(O)<sub>2</sub>R<sub>50a</sub> wherein R<sub>50a</sub> is loweralkyl or aryl, or R<sub>50</sub> and R<sub>51</sub> taken together with the nitrogen atom to which they are attached form a 5- to 7-membered aliphatic heterocycle;
- (ix) -CH<sub>2</sub>OR<sub>52</sub> wherein R<sub>52</sub> is selected from hydrogen, loweralkyl and -C(O)R<sub>53</sub> wherein R<sub>53</sub> is hydrogen, loweralkyl or aryl;
- (x) -CH(OH)R<sub>52a</sub> or -C(O)R<sub>52a</sub> wherein R<sub>52a</sub> is loweralkyl, halo-substituted loweralkyl, -CF<sub>2</sub>COOR<sub>53a</sub> or -CH<sub>2</sub>COOR<sub>53a</sub> wherein R<sub>53a</sub> is hydrogen or a carboxy-protecting group,
- (xii) -CH<sub>2</sub>NR<sub>54</sub>R<sub>55</sub> wherein R<sub>54</sub> is selected from hydrogen, loweralkyl, -C(O)R<sub>56</sub>, -C(O)NR<sub>56</sub>R<sub>57</sub> and -S(O)<sub>2</sub>R<sub>58</sub> wherein R<sub>56</sub> is selected from hydrogen, loweralkyl and aryl and R<sub>58</sub> is selected from lower alkyl and halo-substituted loweralkyl and wherein R<sub>55</sub> and R<sub>57</sub> are independently selected from hydrogen, loweralkyl, hydroxy and alkoxy;
- (xiii) -SO<sub>3</sub>H, -OSO<sub>3</sub>H or -CH<sub>2</sub>SO<sub>3</sub>H,
- (xiv) -OPO<sub>3</sub>H<sub>2</sub>, -PO<sub>3</sub>H<sub>2</sub> or -CH<sub>2</sub>PO<sub>3</sub>H<sub>2</sub>,
- (xv) -SO<sub>2</sub>NR<sub>50</sub>R<sub>51</sub> or -CH<sub>2</sub>SO<sub>2</sub>NR<sub>50</sub>R<sub>51</sub> wherein R<sub>50</sub> and R<sub>51</sub> are defined as above and
- (xvi) -C(O)NHSO<sub>2</sub>R<sub>60</sub>, -C(O)NHC(O)R<sub>60</sub> or -C(O)NHNHSO<sub>2</sub>R<sub>60</sub> wherein R<sub>60</sub> is loweralkyl, halo-substituted loweralkyl or aryl;

with the proviso that one of R<sub>1</sub> and R<sub>1</sub>' is hydrogen, but R<sub>1</sub> and R<sub>1</sub>' are not both hydrogen;

and

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D is



wherein  $R_2$  is independently selected from hydrogen, loweralkyl, carboxy-substituted loweralkyl or alkoxycarbonyl-substituted loweralkyl,

 $R_3$  is

- (i) hydrogen,
- (ii) loweralkyl,
- (iii) halo,
- (iv) halo-substituted loweralkyl,
- (v) thioalkoxy,
- (vi) alkoxy-substituted loweralkyl,
- (vii) thioalkoxy-substituted loweralkyl,
- (viii) aryl,
- (ix) arylalkyl,
- (x)  $-\text{NO}_2$ ,
- (xi)  $-\text{COOR}_8$  wherein  $R_8$  is hydrogen or a carboxy-protecting group,
- (xii)  $-\text{OR}_9$  wherein  $R_9$  is hydrogen, loweralkyl, halo-substituted loweralkyl, aryl, arylalkyl, heterocyclic-substituted loweralkyl or  $-\text{C(O)R}_{10}$  wherein  $R_{10}$  is loweralkyl, halo-substituted loweralkyl,  $-\text{PO}_3\text{H}_2$  or  $-\text{NR}_{11}\text{R}_{12}$  wherein  $R_{11}$  and  $R_{12}$  are independently selected from hydrogen and loweralkyl and
- (xiii)  $-\text{NR}_{13}\text{R}_{14}$  or  $-\text{CH}_2\text{NR}_{13}\text{R}_{14}$  wherein  $R_{13}$  and  $R_{14}$  are

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independently selected from (1) hydrogen, (2) lower alkyl, (3) arylalkyl, (4)  $-C(O)R_{15}$ , (5)  $-S(O)_2R_{15}$  wherein  $R_{15}$  is loweralkyl or halo-substituted loweralkyl and (6)  $-R_{16}-R_{17}$  wherein  $R_{16}$  is alkylene and  $R_{17}$  is (a)  $-NR_{18}R_{19}$  wherein  $R_{18}$  and  $R_{19}$  are independently selected from hydrogen and loweralkyl or (b) unsubstituted or loweralkyl substituted aziridinyl, azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyridinyl or pyrimidinyl, or  $R_{13}$  and  $R_{14}$  taken together with the nitrogen atom to which they are attached form a 5- to 7-membered aliphatic heterocycle and

$R_4$  is

- (i) hydrogen,
- (ii) loweralkyl,
- (iii) halo-substituted loweralkyl,
- (iv)  $-CN$ ,
- (v)  $-NO_2$ ,
- (vi)  $-NH_2$ ,
- (vii)  $-NH-C(=N(R_{25a}))(R_{26a})$  wherein  $R_{25a}$  is hydrogen,  $-CN$  or  $-NO_2$  and  $R_{26a}$  is hydrogen, loweralkyl, alkylamino, dialkylamino, alkoxy or thioalkoxy,
- (viii)  $-NH(R_{26b})$  wherein  $R_{26b}$  is a 5-membered aromatic heterocyclic ring wherein the heterocyclic ring contains 1, 2, 3 or 4 nitrogen atoms or 1 nitrogen atom and 1 oxygen atom or 2 nitrogen atoms and 1 oxygen atom or 1 oxygen atom and 1 sulfur atom and wherein the 5-membered heterocyclic ring is unsubstituted or substituted with a substituent selected from amino, alkylamino, dialkylamino, hydroxy, alkoxy, thioalkoxy, halo, loweralkyl and halo-substituted loweralkyl,
- (ix)  $-CHO$  or  $-CH(=N-OH)$ ,

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- (x) tetrazolyl,
- (xi)  $-\text{NHS}(\text{O})_2\text{R}_{20}$  or  $-\text{CH}_2\text{NHS}(\text{O})_2\text{R}_{20}$  or  $-\text{NHC}(\text{O})\text{R}_{21}$  or  $-\text{N}(\text{OH})\text{C}(\text{O})\text{R}_{21}$  or  $-\text{CH}_2\text{NHC}(\text{O})\text{R}_{21}$  or  $-\text{CH}_2\text{N}(\text{OH})\text{C}(\text{O})\text{R}_{21}$  wherein  $\text{R}_{20}$  is loweralkyl, halo-substituted loweralkyl or  $-\text{NR}_{27a}\text{R}_{27b}$  wherein  $\text{R}_{27a}$  and  $\text{R}_{27b}$  are independently selected from hydrogen,  $-\text{OH}$  and loweralkyl and  $\text{R}_{21}$  is loweralkyl, halo-substituted loweralkyl, amino, alkylamino, dialkylamino or  $-\text{COOH}$ ,
- (xii)  $-\text{CH}(\text{OH})\text{R}_{22}$  or  $-\text{C}(\text{O})\text{R}_{22}$  wherein  $\text{R}_{22}$  is loweralkyl, halo-substituted loweralkyl,  $-\text{CF}_2\text{COOR}_{23}$  or  $-\text{CH}_2\text{COOR}_{23}$  wherein  $\text{R}_{23}$  is hydrogen or a carboxy-protecting group,
- (xiii)  $-\text{COOR}_{24}$  or  $-\text{CH}_2\text{COOR}_{24}$  wherein  $\text{R}_{24}$  is hydrogen or a carboxy-protecting group,
- (xiv)  $-\text{C}(\text{O})\text{NR}_{25}\text{R}_{26}$  or  $-\text{CH}_2\text{C}(\text{O})\text{NR}_{25}\text{R}_{26}$  or  $-\text{NHC}(\text{O})\text{NR}_{25}\text{R}_{26}$  or  $-\text{CH}_2\text{NHC}(\text{O})\text{NR}_{25}\text{R}_{26}$  or  $-\text{NHC}(\text{S})\text{NR}_{25}\text{R}_{26}$  or  $-\text{CH}_2\text{NHC}(\text{S})\text{NR}_{25}\text{R}_{26}$  wherein  $\text{R}_{25}$  and  $\text{R}_{26}$  are independently selected from hydrogen, loweralkyl, hydroxy, alkoxy, hydroxy-substituted loweralkyl, alkoxy-substituted loweralkyl, alkoxy-substituted alkoxy and  $-\text{S}(\text{O})_2\text{R}_{28a}$  wherein  $\text{R}_{28a}$  is loweralkyl or aryl, or  $\text{R}_{25}$  and  $\text{R}_{26}$  taken together with the nitrogen atom to which they are attached form a 5- to 7- membered aliphatic heterocycle;
- (xv)  $-\text{CH}_2\text{OR}_{27}$  wherein  $\text{R}_{27}$  is selected from hydrogen, loweralkyl and  $-\text{C}(\text{O})\text{R}_{28}$  wherein  $\text{R}_{28}$  is hydrogen, loweralkyl or aryl;
- (xvi)  $-\text{CH}_2\text{NR}_{29}\text{R}_{30}$  wherein  $\text{R}_{29}$  is selected from hydrogen, loweralkyl,  $-\text{C}(\text{O})\text{R}_{31}$ ,  $-\text{C}(\text{O})\text{NR}_{31}\text{R}_{32}$  and  $-\text{S}(\text{O})_2\text{R}_{33}$  wherein  $\text{R}_{31}$  is selected from hydrogen, loweralkyl and aryl and  $\text{R}_{33}$  is selected from loweralkyl and halo-substituted loweralkyl and wherein  $\text{R}_{30}$  and  $\text{R}_{32}$  are independently selected from hydrogen, loweralkyl, hydroxy and alkoxy;

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- (xvii)  $-\text{SO}_3\text{H}$ ,  $-\text{OSO}_3\text{H}$  or  $-\text{CH}_2\text{SO}_3\text{H}$ ,
- (xviii)  $-\text{OPO}_3\text{H}$ ,  $-\text{PO}_3\text{H}_2$  or  $-\text{CH}_2\text{PO}_3\text{H}_2$ ,
- (xix)  $-\text{SO}_2\text{NR}_{25}\text{R}_{26}$  or  $-\text{CH}_2\text{SO}_2\text{NR}_{25}\text{R}_{26}$  wherein  $\text{R}_{25}$  and  $\text{R}_{26}$  are defined as above and
- (xx)  $-\text{C}(\text{O})\text{NHSO}_2\text{R}_{59}$ ,  $-\text{C}(\text{O})\text{NHC}(\text{O})\text{R}_{59}$  or  $-\text{C}(\text{O})\text{NHNHSO}_2\text{R}_{59}$  wherein  $\text{R}_{59}$  is loweralkyl, halo-substituted loweralkyl or aryl;

or a pharmaceutically acceptable salt or prodrug thereof.

4. The compound of Claim 3 wherein A is a covalent bond, L, L', M, M' and  $\text{R}_1'$  are hydrogen and -G-E- is  $-\text{CH}_2-\text{N}(\text{R}_5)-$ .

5. A pharmaceutical composition for blocking the interaction of angiotensin II with angiotensin II receptors comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of Claim 1.

6. A pharmaceutical composition for treating hypertension or congestive heart failure comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of Claim 1.

7. A method of blocking the interaction of angiotensin II with angiotensin II receptors comprising administering to a human or other mammal in need a therapeutically effective amount of a compound of Claim 1.

8. A method of treating hypertension or heart failure comprising administering to a human or other mammal in need a therapeutically effective amount of a compound of Claim 1.



## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US93/01177

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) : Please See Extra Sheet.

US CL : 514/212.1; 544/246,56,262,264; 546/113,114,115,183

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/212.1; 544/246, 56, 262, 264; 546/113, 114, 115, 183

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP, A, 0,178,633 (BARGER ET AL.) 23 April 1986, See entire document.	1-8
X	EP, A, 0,411,766 (ALLEN ET AL.) 06 February 1990, See entire document.	1-8
X	EP, A, 0,412,848 (ROBERTS ET AL.) 13 February 1991, See entire document.	1-8
X	EP, A, 0,425,921 (NAKE ET AL.) 08 May 1991, See entire document.	1-8
X	WO, A, 91/07404 (ROBERTS ET AL.) 30 May 1991, See entire document.	1-8

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Further documents are listed in the continuation of Box C.

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See patent family annex.

* Special categories of cited documents:	*T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be part of particular relevance	*X*	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*E* earlier document published on or after the international filing date	*Y*	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*G*	document member of the same patent family
*O* document referring to an oral disclosure, use, exhibition or other means		
*P* document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

21 APRIL 1993

Date of mailing of the international search report

19 MAY 1993

Name and mailing address of the ISA/US  
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# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US93/01177

## A. CLASSIFICATION OF SUBJECT MATTER: IPC (5):

A61K 31/415,31/47,31/495,31/50; C07D

215/233,235/02,235/06,235/12,239/88,239/91,239/94,239/95,239/96,401/12,401/14;403/10, 403/12, 471/04